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| (51) International Patent Classification ⁷ : A61K 45/06, A61P 35/00, A61K 41/00 | | A2 | (11) International Publication Number: WO 00/37107 |
| | | | (43) International Publication Date: 29 June 2000 (29.06.00) |
| (21) International Application Number: PCT/US99/30776 (22) International Filing Date: 22 December 1999 (22.12.99) (30) Priority Data: 60/113,786 23 December 1998 (23.12.98) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MCKEARN, John, P. [US/US]; 18612 Babble Meadows Drive, Glencoe, MO 63038 (US). GORDON, Gary [US/US]; 3282 University Avenue, Highland, IL 60035 (US). CUNNINGHAM, James, J. [CA/US]; 3733 North Bell Avenue, Chicago, IL 60618 (US). GATELY, Stephen, T. [CA/US]; 357 E. Shady Pines Court, Palatine, IL 60067-8800 (US). KOKI, Alane, T. [US/US]; 6689 Highway 185, Beaufort, MO 63013 (US). MASFERRER, Jaime, L. [CL/US]; 1213 Blairshire, Ballwin, MO 63011 (US). (74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). | | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i> |
| (54) Title: METHOD OF USING A CYCLOOXYGENASE-2 INHIBITOR AND A MATRIX METALLOPROTEINASE INHIBITOR AS A COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA | | | |
| (57) Abstract The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor and an antineoplastic agent. | | | |

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**METHOD OF USING A CYCLOOXYGENASE-2 INHIBITOR AND AN
MATRIX METALLOPROTEINASE INHIBITOR AS A COMBINATION
THERAPY IN THE TREATMENT OF NEOPLASIA**

5

Field of the Invention

The present invention relates to combinations and methods for treatment or prevention of neoplasia disorders in a mammal using two or more components with at least one component being an antiangiogenesis agent.

10

Background of the Invention

A neoplasm, or tumor, is an abnormal, unregulated, and disorganized proliferation of cell growth. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness and metastasis. Invasiveness refers to the local spread of a neoplasm by infiltration or destruction of surrounding tissue, typically breaking through the basal laminae that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphatics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance. Cancer is now the second leading cause of death in the United States and over 8,000,000 persons in the United States have been diagnosed with cancer. In 1995, cancer accounted for 23.3% of all deaths in the United States.

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(See U.S. Dept. of Health and Human Services, National Center for Health Statistics, Health United States 1996-97 and Injury Chartbook 117 (1997)).

Cancer is not fully understood on the molecular
5 level. It is known that exposure of a cell to a
carcinogen such as certain viruses, certain chemicals,
or radiation, leads to DNA alteration that inactivates a
"suppressive" gene or activates an "oncogene".
Suppressive genes are growth regulatory genes, which
10 upon mutation, can no longer control cell growth.
Oncogenes are initially normal genes (called
prooncogenes) that by mutation or altered context of
expression become transforming genes. The products of
transforming genes cause inappropriate cell growth. More
15 than twenty different normal cellular genes can become
oncogenes by genetic alteration. Transformed cells
differ from normal cells in many ways, including cell
morphology, cell-to-cell interactions, membrane content,
cytoskeletal structure, protein secretion, gene
20 expression and mortality (transformed cells can grow
indefinitely).

Cancer is now primarily treated with one or a
combination of three types of therapies: surgery,
radiation, and chemotherapy. Surgery involves the bulk
25 removal of diseased tissue. While surgery is sometimes
effective in removing tumors located at certain sites,
for example, in the breast, colon, and skin, it cannot
be used in the treatment of tumors located in other
areas, such as the backbone, nor in the treatment of
30 disseminated neoplastic conditions such as leukemia.

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Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, lung, and testicular cancer.

The adverse effects of systemic chemotherapy used
5 in the treatment of neoplastic disease is most feared by patients undergoing treatment for cancer. Of these adverse effects nausea and vomiting are the most common and severe side effects. Other adverse side effects include cytopenia, infection, cachexia, mucositis in
10 patients receiving high doses of chemotherapy with bone marrow rescue or radiation therapy; alopecia (hair loss); cutaneous complications (see M.D. Abeloff, et al: Alopecia and Cutaneous Complications. P. 755-56. In Abeloff, M.D., Armitage, J.O., Lichter, A.S., and
15 Niederhuber, J.E. (eds) Clinical Oncology. Churchill Livingston, New York, 1992, for cutaneous reactions to chemotherapy agents), such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving radiation or
20 chemotherapy; and reproductive and endocrine complications.

Chemotherapy-induced side effects significantly impact the quality of life of the patient and may dramatically influence patient compliance with
25 treatment.

Additionally, adverse side effects associated with chemotherapeutic agents are generally the major dose-limiting toxicity (DLT) in the administration of these drugs. For example, mucositis, is one of the major dose
30 limiting toxicity for several anticancer agents, including the antimetabolite cytotoxic agents 5-FU,

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methotrexate, and antitumor antibiotics, such as doxorubicin. Many of these chemotherapy-induced side effects if severe, may lead to hospitalization, or require treatment with analgesics for the treatment of
5 pain.

The adverse side effects induced by chemotherapeutic agents and radiation therapy have become of major importance to the clinical management of cancer patients.

10 FR 2,771,005 describes compositions containing a cyclooxygenase-2 inhibitor and a N-methyl-D-aspartate (NMDA) antagonist used to treat cancer and other diseases. WO 99/18,960 describes a combination comprising a cyclooxygenase-2 inhibitor and an induced
15 nitric-oxide synthase inhibitor (iNOS) that can be used to treat colorectal and breast cancer. WO 99/13,799 describes the combination of a cyclooxygenase-2 inhibitor and an opioid analgesic. WO 98/41,511 describes 5-(4-sulphonyl-phenyl)-pyridazinone
20 derivatives used for treating cancer. WO 98/41,516 describes (methylsulphonyl)phenyl-2-(5H)-furanone derivatives that can be used in the treatment of cancer. WO 98/16,227 describes the use of cyclooxygenase-2 inhibitors in the treatment or prevention of neoplasia.
25 WO 97/36,497 describes a combination comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer. WO 97/29,776 describes a composition comprising a cyclooxygenase-2 inhibitor in combination with a leukotriene B4 receptor
30 antagonist and an immunosuppressive drug. WO 97/29,775 describes the use of a cyclooxygenase-2 inhibitor in

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combination with a leukotriene A4 hydrolase inhibitor and an immunosuppressive drug. WO 97/29,774 describes the combination of a cyclooxygenase-2 inhibitor and protstaglandin or antiulcer agent useful in treating

5 cancer. WO 97/11,701 describes a combination comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist useful in treating colorectal cancer. WO 96/41,645 describes a combination comprising a cyclooxygenase-2 inhibitor and a leukotriene A

10 hydrolase inhibitor. WO 96/03,385 describes 3,4,-Di substituted pyrazole compounds given alone or in combination with NSAIDs, steroids, 5-LO inhibitors, LTB4 antagonists, or LTA4 hydrolase inhibitors that may be useful in the treatment of cancer. WO 98/47,890

15 describes substituted benzopyran derivatives that may be used alone or in combination with other active principles. WO 98/16,227 describes a method of using cyclooxygenase-2 inhibitors in the treatment and prevention of neoplasia.

20 U.S. Patent No. 5,854,205 describes an isolated endostatin protein that is an inhibitor of endothelial cell proliferation and angiogenesis. U.S. Patent No. 5,843,925 describes a method for inhibiting angiogenesis and endothelial cell proliferation using a

25 7-[substituted amino]-9-[(substituted glycyloamido]-6-demethyl-6-deoxytetracycline. U.S. Patent No. 5,863,538 describes methods and compositions for targeting tumor vasculature of solid tumors using immunological and growth factor-based reagents in combination with

30 chemotherapy and radiation. U.S. Patent No. 5,837,682 describes the use of fragments of an endothelial cell

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proliferation inhibitor, angiostatin. U.S. Patent No. 5,861,372 describes the use of an aggregate endothelial inhibitor, angiostatin, and its use in inhibiting angiogenesis. U.S. Patent No. 5,885,795 describes
5 methods and compositions for treating diseases mediated by undesired and uncontrolled angiogenesis by administering purified angiostatin or angiostatin derivatives.

PCT/GB97/00650 describes the use of cinnoline
10 derivatives for use in the production of an antiangiogenic and/or vascular permeability reducing effect. PCT/US97/09610 describes administration of an anti-endogin monoclonal antibody, or fragments thereof, which is conjugated to at least one angiogenesis
15 inhibitor or antitumor agent for use in treating tumor and angiogenesis-associated diseases. PCT/IL96/00012 describes a fragment of the Thrombin B-chain for the treatment of cancer. PCT/US95/16855 describes compositions and methods of killing selected tumor cells
20 using recombinant viral vectors.

Ravaud, A. et al. describes the efficacy and tolerance of interleukin-2 (IL-2), interferon alpha-2a, and fluorouracil in patients with metastatic renal cell carcinoma. J.Clin.Oncol. 16, No. 8, 2728-32, 1998.
25 Stadler, W.M. et al. describes the response rate and toxicity of oral 13-cis-retinoic acid added to an outpatient regimen of subcutaneous interleukin-2 and interferon alpha in patients with metastatic renal cell carcinoma. J.Clin.Oncol. 16, No. 5, 1820-25, 1998
30 Rosenbeg, S.A. et al. describes treatment of patients with metastatic melanoma using chemotherapy with

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cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alpha-2b. J.Clin.Oncol. 17, No. 3, 968-75, 1999. Tourani, J-M. et al describes treatment of renal cell carcinoma using
5 interleukin-2, and interferon alpha-2a administered in combination with fluorouracil. J.Clin.Oncol. 16, No. 7, 2505-13, 1998. Majewski, S. describes the anticancer action of retinoids, vitamin D3 and cytokines (interferons and interleukin-12) as related to the
10 antiangiogenic and antiproliferative effects. J.Invest.Dermatol. 108, No. 4, 571, 1997. Ryan, C.W. describes treatment of patients with metastatic renal cell cancer w*ith GM-CSF, Interleukin-2, and interferon-alpha plus oral cis-retinoic acid in patients with
15 metastatic renal cell cancer. J.Invest.Med. 46, No. 7, 274A, 1998. Tai-Ping, D. describes potential anti-angiogenic therapies. Trends Pharmacol.Sci. 16, No. 2, 57-66, 1995. Brembeck, F.H. describes the use of 13-cis retinoic acid and interferon alpha to treat UICC
20 stage III/IV pancreatic cancer. Gastroenterology 114, No. 4, Pt. 2, A569, 1998. Brembeck, F.H. describes the use of 13-cis retinoic acid and interferon alpha in patients with advanced pancreatic carcinoma. Cancer 83, No. 11, 2317-23, 1998. Mackean, M.J. describes the use
25 of roquinimex (Linomide) and alpha interferon in patients with advanced malignant melanoma or renal carcinoma. Br.J.Cancer 78, No. 12, 1620-23, 1998. Jayson, G.C. describes the use of interleukin 2 and interleukin -interferon alpha in advanced renal cancer.
30 Br.J.Cancer 78, No. 3, 366-69, 1998. Abraham, J.M. describes the use of Interleukin-2, interferon alpha and

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5-fluorouracil in patients with metastatic renal carcinoma. Br.J.Cancer 78, Suppl. 2, 8, 1998. Soori, G.S. describes the use of chemo-biotherapy with chlorambucil and alpha interferon in patients with non-

5 hodgkins lymphoma. Blood 92, No. 10, Pt. 2 Suppl. 1, 240b, 1998. Enschede, S.H. describes the use of interferon alpha added to an anthracycline-based regimen in treating low grade and intermediate grade non-

10 hodgkin's lymphoma. Blood 92, No. 10, Pt. 1 Suppl. 1, 412a, 1998. Schachter, J. describes the use of a sequential multi-drug chemotherapy and biotherapy with interferon alpha, a four drug chemotherapy regimen and GM-CSF. Cancer Biother.Radiopharm. 13, No. 3, 155-64, 1998. Mross, K. describes the use of retinoic acid,

15 interferon alpha and tamoxifen in metastatic breast cancer patients. J.Cancer Res. Clin. Oncology. 124 Suppl. 1 R123, 1998. Muller, H. describes the use of suramin and tamoxifen in the treatment of advanced and metastatic pancreatic carcinoma. Eur.J.Cancer 33,

20 Suppl. 8, S50, 1997. Rodriguez, M.R. describes the use of taxol and cisplatin, and taxotere and vinorelbine in the treatment of metastatic breast cancer. Eur.J.Cancer 34, Suppl. 4, S17-S18, 1998. Formenti, C. describes concurrent paclitaxel and radiation therapy in locally

25 advanced breast cancer patients. Eur.J.Cancer 34, Suppl. 5, S39, 1998. Durando, A. describes combination chemotherapy with paclitaxel (T) and epirubicin (E) for metastatic breast cancer. Eur.J.Cancer 34, Suppl. 5, S41, 1998. Osaki, A. describes the use of a combination

30 therapy with mitomycin-C, etoposide, doxifluridine and medroxyprogesterone acetate as second-line therapy for

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advanced breast cancer. Eur.J.Cancer 34, Suppl. 5, S59, 1998.

The use of TNP-470 and minocycline in combination with cyclophosphamide, CDDP, or thiotepa have been
5 observed to substantially increase the tumor growth delay in one pre-clinical solid tumor model. (Teicher, B. A. et al., *Breast Cancer Research and Treatment*, 36: 227-236, 1995). Additionally, improved results were observed when the antiangiogenesis agents were used in
10 combination with cyclophosphamide and fractionated radiation therapy. (Teicher, B. A. et al., *European Journal of Cancer* 32A(14): 2461-2466, 1996).

Neri et al. examined the use of AG-3340 in combination with carboplatin and taxol for the treatment
15 of cancer. (Neri et al., Proc Am Assoc Can Res, Vol 39, 89 meeting, 302 1998). U.S. Patent No. 5,837,696 describes the use of tetracycline compounds to inhibit cancer growth. WO 97/48,685 describes various substituted compounds that inhibit metalloproteases.

20 EP 48/9,577 describes peptidyl derivatives used to prevent tumor cell metastasis and invasion.

WO 98/25,949 describes the use of N5-substituted 5-amino-1,3,4-thiadiazole-2-thiols to inhibit metalloprotease enzymes. WO 99/21,583 describes a
25 method of inhibiting metastases in patients having cancer in which wildtype p53 is predominantly expressed using a combination of radiation therapy and a selective matrix metalloproteinase-2 inhibitor. WO 98/33,768 describes arylsulfonamino hydroxamic acid derivatives
30 in the treatment of cancer.

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WO 98/30,566 describes cyclic sulfone derivatives useful in the treatment of cancer.

WO 98/34,981 describes arylsulfonyl hydroxamic acid derivatives useful in the treatment of cancer.

5 WO 98/33,788 discloses the use of carboxylic or hydroxamic acid derivatives for treatment of tumors.

WO 97/41,844 describes a method of using combinations of angiostatic compounds for the prevention and/or treatment of neovascularization in human
10 patients.

EP 48/9,579 describes peptidyl derivatives with selective gelatinase action that may be of use in the treatment of cancer and to control tumor metastases.

WO 98/11,908 describes the use of carboxylic or
15 hydroxamic acid derivatives and a cyclosporin in combination therapy for treating mammals suffering from arthritic disease.

WO 98/03,516 describes phosphinate based compounds useful in the treatment of cancer.

20 WO 95/23,811 describes novel carbocyclic compounds which inhibit platelet aggregation.

WO 93/24,475 describes sulphamide derivatives may be useful in the treatment of cancer to control the development of metastases.

25 WO 98/16,227 describes a method of using [Pyrozol-1-yl]benzenesulfonamides in the treatment of and prevention of neoplasia.

WO 98/22,101 describes a method of using [Pyrozol-1-yl]benzenesulfonamides as anti-angiogenic agents.

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Description of the Invention

A method for treating or preventing a
5 neoplasia disorder in a mammal, including a human,
in need of such treatment or prevention is
provided. The method comprises treating the mammal
with a therapeutically effective amount of a
combination comprising two or more components, the
10 first component is a cyclooxygenase-2 inhibitor,
the second component is a MMP inhibitor, and the
additional component or components is optionally
selected from (a) an antiangiogenesis agent; (b) an
antineoplastic agent; (c) an adjunctive agent; (d)
15 an immunotherapeutic agent; (e) a device; (f) a
vaccine; (g) an analgesic agent; and (h) a
radiotherapeutic agent; provided that the
additional component(s) is other than the
cyclooxygenase-2 inhibitor selected as the first
20 component and the matrix metalloproteinase
inhibitor selected as the second component.

In one embodiment the combination comprises a
cyclooxygenase-2 inhibitor, a matrix metalloproteinase
inhibitor and an antineoplastic agent.

25 Besides being useful for human treatment, the
present invention is also useful for veterinary
treatment of companion animals, exotic animals and farm
animals, including mammals, rodents, and the like. More
preferred animals include horses, dogs, and cats.

30 The methods and combinations of the present
invention may be used for the treatment or prevention of

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neoplasia disorders including acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, Bartholin gland carcinoma, 5 basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial 10 hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epithelioid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangioblastomas, hemangioendothelioma, 15 hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant 20 melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, 25 osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft 30 tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma,

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submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

5 The methods and combinations of the present invention provide one or more benefits. Combinations of COX-2 inhibitors and MMP inhibitors with the compounds, compositions, agents and therapies of the present invention are useful in treating and preventing
10 neoplasia disorders. Preferably, the COX-2inhibitors and MMP inhibitors or agents and the compounds, compositions, agents and therapies of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally
15 used in clinical situations.

A benefit of lowering the dose of the compounds, compositions, agents and therapies of the present invention administered to a mammal includes a decrease in the incidence of adverse effects associated with
20 higher dosages. For example, by the lowering the dosage of a chemotherapeutic agent such as methotrexate, a reduction in the frequency and the severity of nausea and vomiting will result when compared to that observed at higher dosages. Similar benefits are contemplated
25 for the compounds, compositions, agents and therapies in combination with the COX-2inhibitors and MMP inhibitors of the present invention.

By lowering the incidence of adverse effects, an improvement in the quality of life of a patient
30 undergoing treatment for cancer is contemplated. Further benefits of lowering the incidence of adverse

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effects include an improvement in patient compliance, a reduction in the number of hospitalizations needed for the treatment of adverse effects, and a reduction in the administration of analgesic agents needed to treat pain
5 associated with the adverse effects.

Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

When administered as a combination, the therapeutic
10 agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

When used as a therapeutic the compounds described herein are preferably administered with a
15 physiologically acceptable carrier. A physiologically acceptable carrier is a formulation to which the compound can be added to dissolve it or otherwise facilitate its administration. Examples of physiologically acceptable carriers include, but are not
20 limited to, water, saline, physiologically buffered saline. Additional examples are provided below.

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product.
25 Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions
30 include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences.

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Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, 5 diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, 10 acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the 15 like.

A compound of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or 20 topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or 25 iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical 30 Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975. Another example of includes Liberman, H.A. and

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Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are sold at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules.

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In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated aromatic sulfone hydroximate inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or

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various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can
5 include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and
10 sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

15 The present invention further includes kits comprising a cyclooxygenase-2 inhibitor, a MMP inhibitor, and optionally an antineoplastic agent.

The term "treatment" refers to any process, action, application, therapy, or the like, wherein a mammal,
20 including a human being, is subject to medical aid with the object of improving the mammal's condition, directly or indirectly.

The term "inhibition," in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by
25 delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors,
30 among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention.

The term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be
5 encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia.

10 The term "angiogenesis" refers to the process by which tumor cells trigger abnormal blood vessel growth to create their own blood supply, and is a major target of cancer research. Angiogenesis is believed to be the mechanism via which tumors get needed nutrients to grow
15 and metastasize to other locations in the body. Antiangiogenic agents interfere with these processes and destroy or control tumors.

Angiogenesis is an attractive therapeutic target because it is a multi-step process that occurs in a
20 specific sequence, thus providing several possible targets for drug action. Examples of agents that interfere with several of these steps include thrombospondin-1, angiostatin, endostatin, interferon alpha and compounds such as matrix metalloproteinase
25 (MMP) inhibitors that block the actions of enzymes that clear and create paths for newly forming blood vessels to follow; compounds, such as $\alpha v \beta 3$ inhibitors, that interfere with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor;
30 agents, such as specific COX-2 inhibitors, that prevent the growth of cells that form new blood vessels; and

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protein-based compounds that simultaneously interfere with several of these targets.

Antiangiogenic therapy may offer several advantages over conventional chemotherapy for the treatment of
5 cancer.

Antiangiogenic agents have low toxicity in preclinical trials and development of drug resistance has not been observed (Folkman, J., *Seminars in Medicine of the Beth Israel Hospital, Boston* 333(26): 1757-1763,
10 1995). As angiogenesis is a complex process, made up of many steps including invasion, proliferation and migration of endothelial cells, it can be anticipated that combination therapies will be most effective. Kumar and Armstrong describe anti-angiogenesis therapy used as
15 an adjunct to chemotherapy, radiation therapy, or surgery. (Kumar, CC, and Armstrong, L., Tumor-induced angiogenesis: a novel target for drug therapy?, *Emerging Drugs* (1997), 2, 175-190).

The phrase "therapeutically-effective" is intended
20 to qualify the amount of each agent that will achieve the goal of improvement in neoplastic disease severity and the frequency of neoplastic disease over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

25 A "therapeutic effect" or "therapeutic effective amount" is intended to qualify the amount of an anticancer agent required to relieve to some extent one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the
30 number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably

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stopping) of cancer cell infiltration into peripheral organs; 3) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 4) inhibition, to some extent, of tumor growth; 5) relieving or
5 reducing to some extent one or more of the symptoms associated with the disorder; and/or 6) relieving or reducing the side effects associated with the administration of anticancer agents.

The phrase "combination therapy" (or "co-therapy")
10 embraces the administration of a cyclooxygenase-2 inhibitor, a metalloproteinase inhibitor, and optionally an antineoplastic agent as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial
15 effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time
20 period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that
25 incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time,
30 as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a

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substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other two therapeutic agents of the combination may be administered orally. Alternatively, for example, all three therapeutic agents may be administered orally or all three therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and

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radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic
5 agents, perhaps by days or even weeks.

The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the antiangiogenesis agent and the antineoplastic agent or therapy in the combination therapy, defines a quantity
10 of such agent, or a range of quantity of such agent, that is capable of improving the neoplastic disease severity while reducing or avoiding one or more antineoplastic-agent-induced side effects, such as myelosuppression, cardiac toxicity, alopecia, nausea or
15 vomiting.

The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention, including, but not limited to,
20 those agents, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents; prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation; or reduce the incidence of
25 infection associated with the administration of myelosuppressive anticancer drugs.

The phrase an "immunotherapeutic agent" refers to agents used to transfer the immunity of an immune donor, e.g., another person or an animal, to a host by
30 inoculation. The term embraces the use of serum or gamma globulin containing performed antibodies produced

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by another individual or an animal; nonspecific systemic stimulation; adjuvants; active specific immunotherapy; and adoptive immunotherapy. Adoptive immunotherapy refers to the treatment of a disease by therapy or
5 agents that include host inoculation of sensitized lymphocytes, transfer factor, immune RNA, or antibodies in serum or gamma globulin.

The phrase a "device" refers to any appliance, usually mechanical or electrical, designed to perform a
10 particular function.

The phrase a "vaccine" includes agents that induce the patient's immune system to mount an immune response against the tumor by attacking cells that express tumor associated antigens (TAAs).

15 The phrase "multi-functional proteins" encompass a variety of pro-angiogenic factors that include basic and acid fibroblast growth factors (bFGF and aFGF) and vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) (Bikfalvi, A. et al., *Endocrine*
20 *Reviews* 18: 26-45, 1997). Several endogenous antiangiogenic factors have also been characterized as multi-functional proteins and include angiostatin (O'Reilly et al., *Cell (Cambridge, Mass)* 79(2): 315-328, 1994), endostatin (O'Reilly et al, *Cell (Cambridge,*
25 *Mass)* 88(2): 277-285, 1997), interferon .alpha. (Ezekowitz et al, *N. Engl. J. Med.*, May 28, 326(22) 1456-1463, 1992), thrombospondin (Good et al, *Proc Natl Acad Sci USA* 87(17): 6624-6628, 1990; Tolsma et al, *J Cell Biol* 122(2): 497-511, 1993), and platelet factor 4
30 (PF4) (Maione et al, *Science* 247:(4938): 77-79, 1990).

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The phrase an "analgesic agent" refers to an agent that relieves pain without producing anesthesia or loss of consciousness generally by altering the perception of nociceptive stimuli.

5 The phrase a "radiotherapeutic agent" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia.

10 The term "pBATT" embraces "or "Protein-Based Anti-Tumor Therapies," refers to protein-based therapeutics for solid tumors. The PBATTs are including proteins that have demonstrated efficacy against tumors in animal models or in humans. The protein is then modified to increase its efficacy and toxicity profile by enhancing its bioavailability and targeting.

15 "Angiostatin" is a 38 kD protein comprising the first three or four kringle domains of plasminogen and was first described in 1994 (O'Reilly, M. S. et al., *Cell (Cambridge, Mass.)* 79(2): 315-328, 1994). Mice bearing primary (Lewis lung carcinoma-low metastatic)
20 tumors did not respond to angiogenic stimuli such as bFGF in a corneal micropocket assay and the growth of metastatic tumors in these mice was suppressed until the primary tumor was excised. The factor responsible for the inhibition of angiogenesis and tumor growth was
25 designated mouse angiostatin. Angiostatin was also shown to inhibit the growth of endothelial cells in vitro.

Human angiostatin can be prepared by digestion of plasminogen by porcine elastase (O'Reilly, et al., *Cell* 30 79(2): 315-328, 1994) or with human metalloelastase (Dong et al., *Cell* 88, 801-810, 1997). The angiostatin

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produced via porcine elastase digestion inhibited the growth of metastases and primary tumors in mice.

O'Reilly et al (*Cell* **79**(2): 315-328, 1994) demonstrated that human angiostatin inhibited metastasis of Lewis

5 lung carcinoma in SCID mice. The same group (O'Reilly, M. S. et al., *Nat. Med. (N. Y.)* **2**(6): 689-692, 1996) subsequently showed that human angiostatin inhibited the growth of the human tumors PC3 prostate carcinoma, clone A colon carcinoma, and MDA-MB breast carcinoma in SCID
10 mice. Human angiostatin also inhibited the growth of the mouse tumors Lewis lung carcinoma, T241 fibrosarcoma and M5076 reticulum cell carcinoma in C57Bl mice.

Because these enzymatically-prepared angiostatins are not well characterized biochemically, the precise

15 composition of the molecules is not known.

Angiostatins of known composition can be prepared by means of recombinant DNA technology and expression in heterologous cell systems. Recombinant human

angiostatin comprising Kringle domains one through four

20 (K1-4) has been produced in the yeast *Pichia pastoris* (Sim et al., *Cancer Res* **57**: 1329-1334, 1997). The

recombinant human protein inhibited growth of

endothelial cells in vitro and inhibited metastasis of

Lewis lung carcinoma in C57Bl mice. Recombinant murine

25 angiostatin (K1-4) has been produced in insect cells (Wu et al., *Biochem Biophys Res Comm* **236**: 651-654, 1997).

The recombinant mouse protein inhibited endothelial cell growth in vitro and growth of primary Lewis lung

carcinoma *in vivo*. These experiments demonstrated that

30 the first four kringle domains are sufficient for

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angiostatin activity but did not determine which kringle domains are necessary.

Cao et al. (*J. Biol. Chem.* 271: 29461-29467, 1996), produced fragments of human plasminogen by proteolysis
5 and by expression of recombinant proteins in *E. coli*. These authors showed that kringle one and to a lesser extent kringle four of plasminogen were responsible for the inhibition of endothelial cell growth in vitro. Specifically, kringles 1-4 and 1-3 inhibited at similar
10 concentrations, while K1 alone inhibited endothelial cell growth at four-fold higher concentrations. Kringles two and three inhibited to a lesser extent. More recently Cao et al. (*J Biol Chem* **272**: 22924-22928, 1997), showed that recombinant mouse or human kringle
15 five inhibited endothelial cell growth at lower concentrations than angiostatin (K1-4). These experiments demonstrated in vitro angiostatin-like activity but did not address in vivo action against tumors and their metastases.

20 World patent applications WO 95/29242 A1, WO 96/41194 A1, and WO 96/35774 A2 describe the expression, purification, and characterization of angiostatin. WO 95/29242 A1 951102 discloses purification of a protein from blood and urine by HPLC that inhibits proliferation
25 of endothelial cells. The protein has a molecular weight between 38 kilodaltons and 45 kilodaltons and an amino acid sequence substantially similar to that of a murine plasminogen fragment beginning at amino acid number 79 of a murine plasminogen molecule. WO 96/41194
30 A1 961219, discloses compounds and methods for the diagnosis and monitoring of angiogenesis-dependent

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diseases. WO 96/35774 A2 961114 discloses the structure of protein fragments, generally corresponding to kringle structures occurring within angiostatin. It also discloses aggregate forms of angiostatin, which have
5 endothelial cell inhibiting activity, and provides a means for inhibiting angiogenesis of tumors and for treating angiogenic-mediated diseases.

"Endostatin" is a 20-kDa (184 amino acid) carboxy fragment of collagen XVIII, is an angiogenesis inhibitor
10 produced by a hemangioendothelioma (O'Reilly, M. S. et al., *Cell (Cambridge, Mass.)* 88(2): 277-285, 1997); and WO 97/15666). Endostatin specifically inhibits endothelial proliferation and inhibits angiogenesis and tumor growth. Primary tumors treated with non-refolded
15 suspensions of *E. coli*-derived endostatin regressed to dormant microscopic lesions. Toxicity was not observed and immunohistochemical studies revealed a blockage of angiogenesis accompanied by high proliferation balanced by apoptosis in tumor cells.

20 "Interferon .alpha." (IFN.alpha.) is a family of highly homologous, species-specific proteins that possess complex antiviral, antineoplastic and immunomodulating activities (Extensively reviewed in the monograph "Antineoplastic agents, interferon alfa",
25 American Society of Hospital Pharmacists, Inc., 1996). Interferon .alpha. also has anti-proliferative, and antiangiogenic properties, and has specific effects on cellular differentiation (Sreevalsan, in "Biologic Therapy of Cancer", pp. 347-364, (eds. V.T. DeVita Jr.,
30 S. Hellman, and S.A. Rosenberg), J.B. Lippincott Co, Philadelphia, PA, 1995).

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Interferon .alpha. is effective against a variety of cancers including hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, and Kaposi's sarcoma. The precise mechanism by which IFN.alpha. exerts its anti-tumor activity is not entirely clear, and may differ based on the tumor type or stage of disease. The anti-proliferative properties of IFN.alpha., which may result from the modulation of the expression of oncogenes and/or proto-oncogenes, have been demonstrated on both tumor cell lines and human tumors growing in nude mice (Guttermann, J. U., *Proc. Natl. Acad. Sci., USA* **91**: 1198-1205, 1994).

Interferon is also considered an anti-angiogenic factor, as demonstrated through the successful treatment of hemangiomas in infants (Ezekowitz et al, *N. Engl. J. Med.*, May 28, 326(22) 1456-1463, 1992) and the effectiveness of IFN.alpha. against Kaposi's sarcoma (Krown, *Semin Oncol* 14(2 Suppl 3): 27-33, 1987). The mechanism underlying these anti-angiogenic effects is not clear, and may be the result of IFN.alpha. action on the tumor (decreasing the secretion of pro-angiogenic factors) or on the neo-vasculature. IFN receptors have been identified on a variety of cell types (Navarro et al., *Modern Pathology* 9(2): 150-156, 1996).

United States Patent 4,530,901, by Weissmann, describes the cloning and expression of IFN-.alpha.-type molecules in transformed host strains. United States Patent 4,503,035, Pestka, describes an improved processes for purifying 10 species of human leukocyte interferon using preparative high performance liquid chromatography. United States Patent 5,231,176,

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Goeddel, describes the cloning of a novel distinct family of human leukocyte interferons containing in their mature form greater than 166 and no more than 172 amino acids.

5 United States Patent 5,541,293, by Stabinsky, describes the synthesis, cloning, and expression of consensus human interferons. These are non-naturally occurring analogues of human (leukocyte) interferon-.alpha. assembled from synthetic oligonucleotides. The
10 sequence of the consensus interferon was determined by comparing the sequences of 13 members of the IFN-.alpha. family of interferons and selecting the preferred amino acid at each position. These variants differ from naturally occurring forms in terms of the identity
15 and/or location of one or more amino acids, and one or more biological and pharmacological properties (e.g., antibody reactivity, potency, or duration effect) but retain other such properties.

 "Thrombospondin-1" (TSP-1) is a trimer containing
20 three copies of a 180 kDa polypeptide. TSP-1 is produced by many cell types including platelets, fibroblasts, and endothelial cells (see Frazier, *Curr Opin Cell Biol* 3(5): 792-799, 1991) and the cDNA encoding the subunit has been cloned (Hennessy, et al.,
25 1989, *J Cell Biol* 108(2): 729-736; Lawler and Hynes, *J Cell Biol* 103(5): 1635-1648, 1986). Native TSP-1 has been shown to block endothelial cell migration *in vitro* and neovascularization *in vivo* (Good et al, *Proc Natl Acad Sci USA* 87(17): 6624-6628, 1990). Expression of
30 TSP-1 in tumor cells also suppresses tumorigenesis and tumor-induced angiogenesis (Sheibani and Frazier, *Proc*

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Natl Acad Sci USA 92(15): 6788-6792, 1995; Weinstat-Saslow et al., *Cancer Res* 54(24):6504-6511, 1994). The antiangiogenic activity of TSP-1 has been shown to reside in two distinct domains of this protein (Tolsma et al, *J Cell Biol* 122(2): 497-511, 1993). One of these domains consists of residues 303 to 309 of native TSP-1 and the other consists of residues 481 to 499 of TSP-1. Another important domain consists of the sequence CSVTCG which appears to mediate the binding of TSP-1 to some tumor cell types (Tuszynski and Nicosia, *Bioessays* 18(1): 71-76, 1996). These results suggest that CSVTCG, or related sequences, can be used to target other moieties to tumor cells. Taken together, the available data indicate that TSP-1 plays a role in the growth and vascularization of tumors. Subfragments of TSP-1, then, may be useful as antiangiogenic components of chimeras and/or in targeting other proteins to specific tumor cells. Subfragments may be generated by standard procedures (such as proteolytic fragmentation, or by DNA amplification, cloning, expression, and purification of specific TSP-1 domains or subdomains) and tested for antiangiogenic or anti-tumor activities by methods known in the art (Tolsma et al, *J Cell Biol* 122(2): 497-511, 1993; Tuszynski and Nicosia, *Bioessays* 18(1): 71-76, 1996).

The phrase "integrin antagonist" includes agents that impair endothelial cell adhesion via the various integrins. Integrin antagonists induce improperly proliferating endothelial cells to die, by interfering with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor.

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Adhesion forces are critical for many normal physiological functions. Disruptions in these forces, through alterations in cell adhesion factors, are implicated in a variety of disorders, including cancer, stroke, osteoporosis, restenosis, and rheumatoid arthritis (A. F. Horwitz, *Scientific American*, 276:(5): 68-75, 1997).

Integrins are a large family of cell surface glycoproteins which mediate cell adhesion and play central roles in many adhesion phenomena. Integrins are heterodimers composed of noncovalently linked α and β polypeptide subunits. Currently eleven different α subunits have been identified and six different β subunits have been identified. The various α subunits can combine with various β subunits to form distinct integrins.

One integrin known as $\alpha_v\beta_3$ (or the vitronectin receptor) is normally associated with endothelial cells and smooth muscle cells. $\alpha_v\beta_3$ integrins can promote the formation of blood vessels (angiogenesis) in tumors. These vessels nourish the tumors and provide access routes into the bloodstream for metastatic cells.

The $\alpha_v\beta_3$ integrin is also known to play a role in various other disease states or conditions including tumor metastasis, solid tumor growth (neoplasia), osteoporosis, Paget's disease, humoral hypercalcemia of malignancy, angiogenesis, including tumor angiogenesis, retinopathy, arthritis, including rheumatoid arthritis, periodontal disease, psoriasis, and smooth muscle cell migration (e.g. restenosis).

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Tumor cell invasion occurs by a three step process:
1) tumor cell attachment to extracellular matrix; 2)
proteolytic dissolution of the matrix; and 3) movement
of the cells through the dissolved barrier. This
5 process can occur repeatedly and can result in
metastases at sites distant from the original tumor.

The $\alpha_v\beta_3$ integrin and a variety of other α_v -
containing integrins bind to a number of Arg-Gly-Asp
(RGD) containing matrix macromolecules. Compounds
10 containing the RGD sequence mimic extracellular matrix
ligands and bind to cell surface receptors. Fibronectin
and vitronectin are among the major binding partners of
 $\alpha_v\beta_3$ integrin. Other proteins and peptides also bind the
 $\alpha_v\beta_3$ ligand. These include the disintegrins (M. Pfaff et
15 al., *Cell Adhes. Commun.* 2(6): 491-501, 1994), peptides
derived from phage display libraries (Healy, J.M. et
al., *Protein Pept. Lett.* 3(1): 23-30, 1996; Hart, S.L.
et al., *J. Biol. Chem.* 269(17): 12468-12474, 1994) and
small cyclic RGD peptides (M. Pfaff et al., *J. Biol.*
20 *Chem.*, 269(32): 20233-20238, 1994). The monoclonal
antibody LM609 is also an $\alpha_v\beta_3$ integrin antagonist (D.A.
Cheresh et al., *J. Biol. Chem.*, 262(36): 17703-17711,
1987).

$\alpha_v\beta_3$ inhibitors are being developed as potential
25 anti-cancer agents. Compounds that impair endothelial
cell adhesion via the $\alpha_v\beta_3$ integrin induce improperly
proliferating endothelial cells to die.

The $\alpha_v\beta_3$ integrin has been shown to play a role in
melanoma cell invasion (Seftor et al., *Proc. Natl. Acad.*
30 *Sci. USA*, 89: 1557-1561, 1992). The $\alpha_v\beta_3$ integrin
expressed on human melanoma cells has also been shown to

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promote a survival signal, protecting the cells from apoptosis (Montgomery et al., *Proc. Natl. Acad. Sci. USA*, **91**: 8856-8860, 1994).

Mediation of the tumor cell metastatic pathway by
5 interference with the $\alpha_v\beta_3$ integrin cell adhesion
receptor to impede tumor metastasis would be beneficial.
Antagonists of $\alpha_v\beta_3$ have been shown to provide a
therapeutic approach for the treatment of neoplasia
(inhibition of solid tumor growth) because systemic
10 administration of $\alpha_v\beta_3$ antagonists causes dramatic
regression of various histologically distinct human
tumors (Brooks et al., *Cell*, **79**: 1157-1164, 1994).

The adhesion receptor identified as integrin $\alpha_v\beta_3$ is
a marker of angiogenic blood vessels in chick and man.
15 This receptor plays a critical role in angiogenesis or
neovascularization. Angiogenesis is characterized by
the invasion, migration and proliferation of smooth
muscle and endothelial cells by new blood vessels.
Antagonists of $\alpha_v\beta_3$ inhibit this process by selectively
20 promoting apoptosis of cells in the neovasculature. The
growth of new blood vessels, also contributes to
pathological conditions such as diabetic retinopathy
(Adonis et al., *Amer. J. Ophthalmol.*, **118**: 445-450, 1994)
and rheumatoid arthritis (Peacock et al., *J. Exp. Med.*,
25 **175**:, 1135-1138, 1992). Therefore, $\alpha_v\beta_3$ antagonists can
be useful therapeutic targets for treating such
conditions associated with neovascularization (Brooks et
al., *Science*, **264**: 569-571, 1994).

The $\alpha_v\beta_3$ cell surface receptor is also the major
30 integrin on osteoclasts responsible for the attachment
to the matrix of bone. Osteoclasts cause bone

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resorption and when such bone resorbing activity exceeds bone forming activity, osteoporosis (a loss of bone) results, which leads to an increased number of bone fractures, incapacitation and increased mortality.

- 5 Antagonists of $\alpha_v\beta_3$ have been shown to be potent inhibitors of osteoclastic activity both *in vitro* (Sato et al., *J. Cell. Biol.*, **111**: 1713-1723, 1990) and *in vivo* (Fisher et al., *Endocrinology*, **132**: 1411-1413, 1993). Antagonism of $\alpha_v\beta_3$ leads to decreased bone
- 10 resorption and therefore assists in restoring a normal balance of bone forming and resorbing activity. Thus it would be beneficial to provide antagonists of osteoclast $\alpha_v\beta_3$ which are effective inhibitors of bone resorption and therefore are useful in the treatment or prevention
- 15 of osteoporosis.

PCT Int. Appl. WO 97/08145 by Sikorski et al., discloses meta-guanidine, urea, thiourea or azacyclic amino benzoic acid derivatives as highly specific $\alpha_v\beta_3$ integrin antagonists.

- 20 PCT Int. Appl. WO 96/00574 A1 960111 by Cousins, R.D. et. al., describe preparation of 3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine and -2-benzazepine derivatives and analogs as vitronectin receptor antagonists.

- 25 PCT Int. Appl. WO 97/23480 A1 970703 by Jadhav, P.K. et. al. describe annelated pyrazoles as novel integrin receptor antagonists. Novel heterocycles including 3-[1-[3-(imidazolin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2-(benzyl oxycarbonylamino)propionic
- 30 acid, which are useful as antagonists of the $\alpha_v\beta_3$ integrin and related cell surface adhesive protein

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receptors.

PCT Int. Appl. WO 97/26250 A1 970724 by Hartman, G.D. et al., describe the preparation of arginine dipeptide mimics as integrin receptor antagonists.

- 5 Selected compounds were shown to bind to human integrin $\alpha_v\beta_3$ with EIB <1000 nM and claimed as compounds, useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets.

- 10 PCT Int. Appl. WO 97/23451 by Diefenbach, B. et. al. describe a series of tyrosine-derivatives used as α_v -integrin inhibitors for treating tumors, osteoporosis, osteolytic disorder and for suppressing angiogenesis.

- 15 PCT Int. Appl. WO 96/16983 A1 960606. by Vuori, K. and Ruoslahti, E. describe cooperative combinations of $\alpha_v\beta_3$ integrin ligand and second ligand contained within a matrix, and use in wound healing and tissue regeneration. The compounds contain a ligand for the $\alpha_v\beta_3$ integrin and a ligand for the insulin receptor, the PDGF receptor, the IL-4 receptor, or the IGF receptor, combined in a biodegradable polymeric (e.g. hyaluronic acid) matrix.
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- PCT Int. Appl. WO 97/10507 A1 970320 by Ruoslahti, E; and Pasqualini, R. describe peptides that home to a selected organ or tissue in vivo, and methods of identifying them. A brain-homing peptide, nine amino acid residues long, for example, directs red blood cells to the brain. Also described is use of *in vivo* panning to identify peptides homing to a breast tumor or a melanoma.
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PCT Int. Appl. WO 96/01653 A1 960125 by Thorpe, Philip E.; Edgington, Thomas S. describes bifunctional ligands for specific tumor inhibition by blood coagulation in tumor vasculature. The disclosed
5 bispecific binding ligands bind through a first binding region to a disease-related target cell, e.g. a tumor cell or tumor vasculature; the second region has coagulation-promoting activity or is a binding region for a coagulation factor. The disclosed bispecific
10 binding ligand may be a bispecific (monoclonal) antibody, or the two ligands may be connected by a (selectively cleavable) covalent bond, a chemical linking agent, an avidin-biotin linkage, and the like. The target of the first binding region can be a
15 cytokine-inducible component, and the cytokine can be released in response to a leukocyte-activating antibody; this may be a bispecific antibody which crosslinks activated leukocytes with tumor cells.

The phrase "matrix metalloproteinase inhibitor" or
20 "MMP inhibitor" includes agents that specifically inhibit a class of enzymes, the zinc metalloproteinases (metalloproteases). The zinc metalloproteinases are involved in the degradation of connective tissue or connective tissue components. These enzymes are
25 released from resident tissue cells and/or invading inflammatory or tumor cells. Blocking the action of zinc metalloproteinases interferes with the creation of paths for newly forming blood vessels to follow. Examples of MMP inhibitors are described in Golub, LM,
30 Inhibition of Matrix Metalloproteinases: Therapeutic Applications (Annals of the New York Academy of Science,

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Vol 878). Robert A. Greenwald and Stanley Zucker (Eds.), June 1999), and is hereby incorporated by reference. Connective tissue, extracellular matrix constituents and basement membranes are required components of all

5 mammals. These components are the biological materials that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen,

10 elastin, proteoglycans, fibronectin and laminin. These biochemicals makeup, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor. Under normal conditions, connective tissue turnover

15 and/or repair processes are controlled and in equilibrium. The loss of this balance for whatever reason leads to a number of disease states. Inhibition of the enzymes responsible loss of equilibrium provides a control mechanism for this tissue decomposition and,

20 therefore, a treatment for these diseases.

Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major

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class of enzymes involved in this function are the zinc metalloproteinases (metalloproteases).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14). MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by metalloproteases is a feature of many pathological conditions. Examples include rheumatoid arthritis, osteoarthritis, septic arthritis; corneal, epidermal or gastric ulceration; tumor metastasis, invasion or angiogenesis; periodontal disease; proteinuria; Alzheimer's Disease; coronary thrombosis and bone disease. Defective injury repair processes also occur. This can produce improper wound healing leading to weak repairs, adhesions and scarring. These latter defects can lead to disfigurement and/or permanent disabilities as with post-surgical adhesions.

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Matrix metalloproteases are also involved in the biosynthesis of tumor necrosis factor (TNF) and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF- α , for example, is a cytokine that at present is thought to be produced initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large integer of deleterious effects *in vitro* and *in vivo*. For example, TNF can cause and/or contribute to the effects of inflammation, rheumatoid arthritis, autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis, cardiovascular/pulmonary effects such as post-ischemic reperfusion injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during shock such as septic shock and hemodynamic shock. Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal.

TNF- α convertase is a metalloproteinase involved in the formation of active TNF- α . Inhibition of TNF- α convertase inhibits production of active TNF- α . Compounds that inhibit both MMPs activity have been disclosed in, for example PCT Publication WO 94/24140. Other compounds that inhibit both MMPs activity have also been disclosed in WO 94/02466. Still other compounds that inhibit both MMPs activity have been disclosed in WO 97/20824.

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There remains a need for effective MMP and TNF- α convertase inhibiting agents. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994)). McGeehan et al., *Nature* 376, 558-561 (1994) also reports such findings.

MMPs are involved in other biochemical processes in mammals as well. Included is the control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β -Amyloid Precursor Protein) to the amyloid plaque and inactivation of α_1 -protease inhibitor (α_1 -PI). Inhibition of these metalloproteases permits the control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as α_1 -PI supports the treatment and prevention of diseases such as emphysema, pulmonary diseases, inflammatory diseases and diseases of aging such as loss of skin or organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin (MMP-3), gelatinase (MMP-2), or collagenase III (MMP-13) are the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile.

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Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitor of metalloproteinase (TIMP), α_2 -macroglobulin and their analogs or derivatives. These are high molecular weight protein molecules that form inactive complexes with metalloproteases. An integer of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the production of angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO 95/12389. Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are also shown in WO 96/11209. Still further Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are shown in U.S. Patent No. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications that disclose carbon back-boned compounds, such as in WO 95/29892. Other published patents include WO 97/24117. Additionally, EP 0 780 386 further discloses hydroxamate group-containing MMP inhibitors. WO 90/05719 disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones. WO 93/20047 also discloses hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones. Additionally, WO 95/09841 discloses disclose hydroxamates that have

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peptidyl back-bones or peptidomimetic back-bones. And
WO 96/06074 further discloses hydroxamates that have
peptidyl back-bones or peptidomimetic back-bones.

Schwartz et al., *Progr. Med. Chem.*, 29:271-334 (1992)

- 5 also discloses disclose hydroxamates that have peptidyl
back-bones or peptidomimetic back-bones. Furthermore,
Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75. (1997)
discloses hydroxamates that have peptidyl back-bones or
peptidomimetic back-bones. Also, Denis et al., *Invest.*
10 *New Drugs*, 15(3): 175-185 (1997) discloses hydroxamates
that have a peptidyl back-bones or peptidomimetic back-
bones as well.

- One possible problem associated with known MMP
inhibitors is that such compounds often exhibit the same
15 or similar inhibitory effects against each of the MMP
enzymes. For example, the peptidomimetic hydroxamate
known as batimastat is reported to exhibit IC₅₀ values
of about 1 to about 20 nanomolar (nM) against each of
MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat,
20 another peptidomimetic hydroxamate was reported to be
another broad-spectrum MMP inhibitor with an enzyme
inhibitory spectrum very similar to batimastat, except
that marimastat exhibited an IC₅₀ value against MMP-3 of
230 nM. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-
25 75 (1997).

- Meta analysis of data from Phase I/II studies using
marimastat in patients with advanced, rapidly
progressive, treatment-refractory solid tumor cancers
(colorectal, pancreatic, ovarian, prostate), indicated a
30 dose-related reduction in the rise of cancer-specific
antigens used as surrogate markers for biological

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activity. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

10 In view of the importance of hydroxamate MMP inhibitor compounds in the treatment of several diseases and the lack of enzyme specificity exhibited by two of the more potent drugs now in clinical trials, it would be beneficial to use hydroxamates of greater enzyme
15 specificity. This would be particularly the case if the hydroxamate inhibitors exhibited limited inhibition of MMP-1 that is relatively ubiquitous and as yet not associated with any pathological condition, while exhibiting quite high inhibitory activity against one or
20 more of MMP-2, MMP-9 or MMP-13 that are associated with several pathological conditions.

Non-limiting examples of matrix metalloproteinase inhibitors that may be used in the present invention are
25 identified in Table No. 1, below.

Table No. 1. Matrix metalloproteinase inhibitors.

| Compound | Trade Name | Reference | Dosage |
|---|----------------------------------|---|---|
| Biphenyl hydroxamate | | WO 97/18188 | |
| | AG-3067 (Agouron Pharm. Inc.) | Winter Conf. Med. Bio-organic Chem. 1997 January, 26-31 | |
| | AG-3340 (Agouron Pharm. Inc.) | WO 97/20824 | 50 mg/kg treatment of Lewis lung carcinomas in test animals |
| | AG-2024 (Agouron Pharm. Inc.) | | |
| | AG-3365 (Agouron Pharm. Inc.) | | |
| 3(S)-N-hydroxy-4-(4-[4-(imidazol-1-yl)phenoxy]benzenesulfonyl)-2,2- | | WO 97/20824. FEBS (1992) 296 (3):263 | In female Lewis rats, arthritis model: dose of 25 |

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| Compound | Trade Name | Reference | Dosage |
|--|----------------------------------|--|--|
| dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide, and derivatives thereof | | | mg/kg/day gave 97.5% weight loss inhibition |
| Heteroaryl succinamides derivatives | | WO 98/17643 | |
| | AG-3296 (Agouron Pharm. Inc.) | | |
| | AG-3287 (Agouron Pharm. Inc.) | | |
| | AG-3293 (Agouron Pharm. Inc.) | | |
| | AG-3294 (Agouron Pharm. Inc.) | | |
| | AG-3067 (Agouron Pharm. Inc.) | Winter Conf Med Bio-organic Chem 1997 January 26-31 | |

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| Compound | Trade Name | Reference | Dosage |
|---|------------|-------------|--------|
| 2R,4S)-4-hydroxy-2-isobutyl-5-mercapto-N-[(1S)-2,2-dimethyl-1-methylcarbamoylpropyl]pentanamide | | EP 0818443 | |
| N-alkyl, N-phenylsulfonyl-N'-hydroxamic acid derivatives of heteroaryl carboxylic acids | | WO 98/16520 | |
| Novel N-alkyl, N-phenylsulfonyl-N'-hydroxamic acid derivatives of heteroaryl carboxylic acids | | WO 98/16514 | |
| Novel N-alkyl, N-phenylsulfonyl-N'-hydroxamic acid derivatives of cycloalkane carboxylic acids | | WO 98/16506 | |
| Novel N-alkyl, | | WO 98/16503 | |

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| Compound | Trade Name | Reference | Dosage |
|--|------------|---|--------|
| N-phenylsulfonyl-N'-hydroxamic acid derivatives of anthranilic acid | | | |
| sulfonamido-hydroxamic acid derivatives | | EP 03/98753 | |
| TIMP-3: polynucleotides encoding endogenous (human) peptides | | WO 95/09918 | |
| (3alpha, 5beta, 6alpha, 7alpha, 8alpha)-4', 4'-bis(2, 2-dimethyl-1, 3-benzodioxole-5, 6-diyl)bis(2, 6-piperazinedione) and derivatives thereof | | WO 93/23075 | |
| | BE-16627B | WO 91/08222. Int. J. Cancer 1994 58 5 730 - 735 | |
| (2S)-4-(4-(4- | | WO 96/15096 | |

| Compound | Trade Name | Reference | Dosage |
|--|-------------|-------------------------------------|-----------------------------|
| chlorophenyl)phenyl)-4-oxo- 2-(2-phthalimidoethyl)butanoic acid | | | |
| | Bay-12-9566 | WO 96/15096 | 10 to 400 mg/day |
| 4-oxo-2-(2-phthalimidoethyl) alkanolic acid derivatives | | WO 97/43238 | |
| Novel 4-(4-Alkynylphenyl) 4-oxobutanoic acid derivatives | | WO 97/43237 | |
| Substituted 4-biarylbutyric or 5-biarylpentanoic acids and derivatives | | WO 96/15096 | |
| Substituted 4-biphenyl-4-hydroxybutyric acid derivatives | | WO 98/22436 | |
| 2R,S)-HONH-CO-CH(i-Bu)-CO-Ala-Gly-NH ₂ , | | J Med Chem 1998 41 3 339 -345 | |
| batimastat; BB-94; Hydroxamic | | WO 90/05719 | 15 to 135 mg/m ² |

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| Compound | Trade Name | Reference | Dosage |
|--|------------------------|---|---------------------------------------|
| acid based collagenase inhibitors | | | administer- ed intra- pleurally |
| Hydroxamic acid based collagenase inhibitors | | WO 90/05719 | |
| marimastat BB- 2516; Hydroxamic acid derivatives | | WO 94/02447 | 5 to 800 mg daily |
| alpha-cycloalkyl analogs of marimastat | | Bio-organic Med Chem Lett 1998 8 11 1359 - 1364 | |
| | GI-245402 (BB-2983) | | |
| Hydroxamic acid derivatives | | WO 94/21625 | |
| Succinyl hydroxamic acid, N-formyl-N- hydroxy amino carboxylic acid and succinic acid amide derivatives | | WO 95/32944 | |
| hydroxamic acid, N-formyl-N- hydroxyamino and | | WO 97/19053 | |

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| Compound | Trade Name | Reference | Dosage |
|---|------------|--|--------|
| carboxylic acid derivatives, | | | |
| pseudopeptide hydroxamic and carboxylic acid derivatives from the corresponding lactone and alpha-amino acid | | WO 97/19050 | |
| Succinic acid amide derivatives | | WO 97/03966. GB 95/00111. GB 95/00121. | |
| Hydroxamic acid derivatives | | WO 97/02239 | |
| Succinamidyl (alpha substituted) hydroxamic acid derivatives | | WO 96/33165 | |
| (2S,3R)-3-[2,2-dimethyl-1S-(thiazol-2-ylcarbamoyl)propylcarbamoyl]-5-methyl-2-(prop-2-enyl)hexano-hydroxamic acid and derivatives thereof | | WO 96/25156 | |

| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|--------|
| Hydroxamic or carboxylic acid derivatives | | WO 96/16931 | |
| hydroxamic and carboxylic acids | | WO 96/06074 | |
| 2-[(1S)-1-((1R)-2-[[1,1'-biphenyl]-4-ylmethylthio]-1-[(1S)-2,2-dimethyl-1-(methylcarbamoyl)propylcarbamoyl]ethylcarbamoyl)-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butylthio]-acetate, and derivatives thereof | | WO 98/23588 | |
| Hydroxamic acid derivatives as inhibitors of cytokine production | | WO 95/09841 | |
| Hydroxamic acid derivatives | | WO 94/24140 | |
| Aromatic or heteroaryl | | WO 95/19956 | |

| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|--|
| substituted hydroxamic or carboxylic acid derivatives | | | |
| Hydroxamic acid derivatives | | WO 95/19957 | Doses are preferably 1 to 100 mg/kg. |
| Hydroxamic acid and carboxylic acid derivatives | | WO 95/19961 | Doses are preferably 1 to 100 mg/kg. |
| Butanediamide, N1- [1(cyclohexyl- methyl)-2 (methylamino)-2- oxoethyl]-N4,3- dihydroxy-2-(2- methylpropyl)-, [2R[N1(S*), 2R*, 3 S*]]- | BB-1433 | | At 50 mg/kg bid. p.o. inhibited bone mineral density loss |
| tetracycline analogs and D- penicillamine | | EP 733369 | D-penicill- amine reduced allergic encephaliti s symptom scores in a dose |

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| Compound | Trade Name | Reference | Dosage |
|-------------------------|------------|--|---|
| | | | dependent manner at 27, 125 and 375 mug with complete inhibition |
| | CDP-845 | Biochem Pharmacol 1990 39 12 2041-2049 | |
| succinamide derivatives | | WO 95/04033 | oral bioavail-ability by murine pleural cavity assay in the presence of gelatinase: Between 73% and 100% inhibition was displayed at 10 mg/kg for six of the compounds. |

| Compound | Trade Name | Reference | Dosage |
|---|------------|--|--|
| | | | The seventh displayed 100% inhibition at 80 mg/kg. |
| Peptidyl derivatives | | WO 94/25435. WO 94/25434 | |
| Mercaptoalkyl-peptidyl compounds having an imidazole substituent | | WO 97/19075 | |
| mercaptoalkyl-peptide derivatives | | WO 97/38007. WO 95/12389. WO 96/11209. | |
| Mercaptoalkyl-amide derivatives | | WO 97/37974 | |
| arylsulfonyl-hydrazine derivatives | | WO 97/37973. WO 95/12389 | |
| N-acetylthio-lacetyl-N-(3-phthalimidopropyl)-L-leucyl-L-phenylalanine N-methylamide | | WO 96/35714 | |
| 2-acetylsulfany-1-5-phthalimido- | | WO 96/35712 | dosages of about 0.5 |

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| Compound | Trade Name | Reference | Dosage |
|---|------------|-------------|---|
| pentanoyl-L-leucineN-(2-phenylethyl)-amide | | | mg to 3.5 g per day for the treatment of inflammation |
| 5-phthalimido-pentanoyl-L-leucyl-L-phenylalanineN-methylamide | | WO 96/35711 | |
| peptidyl derivatives | | WO 98/06696 | |
| 4-[4-(methoxycarbonyl methoxy)-3,5-dimethylphenyl]-2-methyl-1(2H)-phthalazinone, and hydroxamic and carboxylic acid derivatives | | WO 98/05635 | |
| thio-substituted peptides | | WO 97/12902 | |
| Mercaptoamides | | WO 97/12861 | |
| Peptidyl derivatives having SH or acylo groups which are | | WO 96/35687 | |

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| Compound | Trade Name | Reference | Dosage |
|--|--|-------------|--------|
| amides, primary amides or thioamides | | | |
| | D-5410 (Chiro- science Group plc) | | |
| | | WO 95/13289 | |
| | CH-104, (Chiro- science Group plc) | | |
| | D-2163 (Chiro Science Ltd.) | | |
| | D-1927 (Chiro Science Ltd.) | | |
| | Dermastat (Colla- Genex Phar- maceu- tical Inc.) | | |
| | Metastat (Colla- Genex) | | |

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| Compound | Trade Name | Reference | Dosage |
|---|--|-------------|--|
| | Osteostat (Colla- Genex Phar- maceu- tical Inc.) | | |
| | doxy- cycline; Roche; Periostat | | Gingival crevicular fluid collagenase is reported to be inhibited at concentra- tions of 5- 10 microg /ml or 15- 30 microM |
| 2S, 5R, 6S-3- aza-4-oxo-10- oxa-5-isobutyl- 2-(N- methylcarbox- amido)- [10]paracyclopha- ne-6-N- hydroxycarboxami- de | | WO 97/18207 | |

| Compound | Trade Name | Reference | Dosage |
|---|--|--|--------|
| hydroxamic acid and amino- carboxylate compounds | | WO 96/33176 | |
| N-hydroxamic derivatives of succinamide | | WO 96/33166 | |
| Macrocyclic amino carboxylates | | J Med Chem 1998 41 11 1749-1751 | |
| | SE-205 (Du Pont Merck Pharm Co.) | Bio-organic Med Chem Lett 1998 8 7 837-842. J Med Chem 1998 41 11 1745 -1748 | |
| macrocyclic matrix metalloprotease- 8 inhibitors | | | |
| Hydroxamic acid and carboxylic acid derivatives | | WO 95/22966 | |
| succinamid derivatives | | US 5256657 | |
| mercaptosulfide derivatives | | WO 95/09833 | |
| sulfoximine and sulfodiimine | | WO 95/09620 | |

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| Compound | Trade Name | Reference | Dosage |
|---|-----------------------|---|-------------------------|
| derivatised peptides | | | |
| water soluble MMP inhibitors | | WO 96/33968 | |
| hydantoin derivatives | | EP 06/40594 | |
| Piperazine derivatives | | WO 98/27069 | |
| | GI-155704A | J Med Chem 1994 37 5 674. Bioorganic Med Chem Lett 1996 6 16 1905 - 1910 | |
| Cyclic imide derivatives. | | EP 05/20573 | |
| 3-(mercapto-methyl) hexahydro-2,5-pyrazinedione derivatives | | WO 97/48685 | |
| beta-mercaptoketone and beta-mercaptoalcohol derivatives | | WO 96/40738 | |
| | ilomastat MPI; GM- | US 5114953. Cancer Res | eye drops containing |

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| Compound | Trade Name | Reference | Dosage |
|--|-------------------------------------|-------------------------|---------------------------------|
| | 6001; Galardin | 1994 54 17 4715-4718 | ilomastat (800 microg/ml) |
| Cyclic and heterocyclic N- substituted alpha- iminohydroxamic and carboxylic acids | | WO 97/18194 | |
| Aminomethyl- phosphonic and aminomethyl- phosphinic acids derivatives | | EP 703239 | |
| 3-Mercapto- acetylamino-1,5- substituted-2- oxo-azepan derivatives | | WO 98/12211 | |
| 2-substituted indane-2- mercaptoacetyl- amide tricyclic derivatives | | WO 94/04531 | |
| | Ro-2756 (Roche Holding AG) | | |
| | Ro-26-4325 | | |

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| Compound | Trade Name | Reference | Dosage |
|---|----------------------------------|--|--------------------------------------|
| | (Roche Holding AG) | | |
| | Ro-26-5726 (Roche Holding AG) | | |
| | Ro-26-6307 (Roche Holding AG) | | |
| | Ro-31-9790 (Roche Holding AG) | J Am Soc Nephrol 1995 6 3 904. Inflamm Res 1995 44 8 345 -349 | mono-arthritis in rat: 100 mg/kg/day |
| substituted and unsubstituted hydroxamates (specifically N-[D,L-2-isobutyl-3-(N'-hydroxy-carbonyl-amido)-propanoyl]tryptophanmethanamide) | | WO 92/09556 | |
| GM6001, N-(2(R)-2-(hydroxyaminocarbonylmethyl)-4- | | WO 95/24921 | |

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| Compound | Trade Name | Reference | Dosage |
|---|--|-------------------------------------|--------|
| methylpentanoyl) -L-tryptophan methylester. | | | |
| Oligonucleotide (c-jun) | | | |
| Sulfated polysaccharides | | WO 98/11141 | |
| | KB-R7785; KB-R8301; KB-R8845 | Life Sci 1997 61 8 795-803 | |
| Fas ligand solubilization inhibitor | | WO 97/09066 | |
| gelastatin AB, KRIBB | | | |
| | KT5-12 (Kotobuki Seiyaku Co Ltd.) | Faseb J 1998 12 5 A773 (4482) | |
| 2-(N2-[(2R)-2- (2-hydroxyamino- 2-oxoethyl)-5- (4- methoxyphenoxy)p entanoyl]-L- phenylalanylamin o)ethanesulfonam ide, and carboxylic acid derivatives | | GB 23/18789 | |

| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|--|
| thereof | | | |
| Chromone derivatives | | EP 758649 | 2-Pyrolylthio-chromone in a murine melanoma model produced 37% inhibition at 100 mg/kg |
| Esculetin derivatives, | | EP 719770 | |
| substituted and unsubstituted hydroxyureas and reverse hydroxamates | | WO 92/09563 | |
| Synthetic MMP inhibitors (ex. N-(D,L-2-isobutyl-3-(N'-hydroxycarbonylamido)propanoyl)tryptophan methylamide) | | WO 94/22309 | |
| Reverse hydroxamates and hydroxyureas | | WO 95/19965 | in female mice infected |

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| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|---|
| | | | w/murine melanoma - init 80 mu g followed by 150 mg/kg/day |
| N-(mercaptoacyl)- aryl derivatives of leucine and phenylalanine | | US 5629343 | |
| N-carboxyalkyl derivatives | | WO 95/29689 | |
| Substituted cyclic derivatives | | GB 22/82598 | Inflammatio n is stated to be effectively treated by oral administrat ion of 0.01 to 50 mg/kg |
| Substituted n- carboxyalkyldi- peptides | | GB 22/72441 | |
| (2S,4R)-2- methyl-4- (phenylamino- carbonylmethyl- aminocarbonyl)- | | WO 97/11936 | |

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| Compound | Trade Name | Reference | Dosage |
|---|---|-------------|------------|
| 6-(4-propyl-phenyl)hexanoic acid, and carboxylic acid derivatives | | | |
| Substituted cyclic derivatives | | US 5403952 | |
| Thiol sulfonamide metalloprotease inhibitors | | WO 98/03166 | |
| Thiol sulfone metalloproteinase inhibitors | | WO 98/03164 | |
| formulations containing vanadium compounds and N-acetylcysteine | | WO 97/47296 | |
| | NSC-683551; COL-3 (National Cancer Institute) | | |
| | BB-3644 (Neures Ltd.) | | |
| Arylsulfonamido- | CGS- | Int Congr | 600 mg tid |

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| Compound | Trade Name | Reference | Dosage |
|---|----------------------|---|--|
| substituted hydroxamic acids | 27023A; CGS-25966 | Inflamm Res Assoc 1994 7th Abs 73. EP-00606046 | (Ph I - colorectal and melanoma patients); 100 mg/kg in food in osteoarthri tis model rabbits |
| alpha- Substituted arylsulfonamido hydroxamic acid derivatives | | WO 97/22587 | |
| Arylsulfonamido- substituted hydroxamic acids | | US 5455258 | active at 30 mg/kg in in vivo assay |
| Arylsulfonamido- substituted hydroxamic acids | | WO 96/00214 | |
| 2S,3S)-N- hydroxy-5- methyl-2-[2-(2- methoxyethoxy)et hoxymethyl]-3- (N-[(1S)-1-(N- methylcarbamoyl) -2- | | WO 98/14424 | |

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| Compound | Trade Name | Reference | Dosage |
|---|------------|---|--|
| phenylethyl]carb amoyl)hexanamide and Hydroxamic acid deriva- tives | | | |
| arylsulfonamido- substituted hydroxamic acids | | WO 96/40101 | in tumor model mice: administere d for 7 to 17 days at a dosage of 30 mg/kg twice daily |
| Aryl (sulfide, sulfoxide and sulfone) derivatives | | WO 97/49679 | |
| Phenylsulfon- amide derivatives | | WO 97/45402 | |
| Arylsulfonamido- aminoacid derivative | | EP 757037 | |
| AlPDX (Oregon Health Sciences University) | | | |
| futoenone analogs | | Bio-organic Med Chem Lett 1995 5 15 1637 - | |

| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|--------------------------|
| | | 1642 | |
| debromohymeni- aldisine and related compounds | | WO 96/40147 | preferred 1-30 mg/day |
| amide derivatives of 5-amino-1,3,4- thiadiazolones | | WO 96/40745 | |
| 3S-(4-(N- hydroxylamino)- 2R- isobutylsuccinyl)amino-1- methoxymethyl- 3,4- dihydrocarbostyr il and derivatives thereof | | WO 94/21612 | |
| Carbostyryl derivatives | | JP 8325232 | |
| OPB-3206 (Otsuka Pharmaceutical Co, Ltd.) | | | |
| Arylsulfonyl hydroxamic acid derivatives | | WO 96/33172 | |
| Cyclic sulfone derivatives | | EP 818442 | |

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| Compound | Trade Name | Reference | Dosage |
|---|------------|-------------|--------|
| arylsulfonamido N-hydroxamic acid derivatives of butyric acid | | WO 96/27583 | |
| Arylsulfonyl- amino hydroxamic acid derivatives | | WO 98/07697 | |
| phosphinate- based derivatives | | WO 98/03516 | |
| cyclopentyl- substituted glutaramide derivatives | | WO 92/14706 | |
| N-hydroxamic acid succinamide derivatives | | WO 97/49674 | |
| Thiadiazole amide MMP inhibitors. | | WO 97/48688 | |
| (S)-1-[2- [[[(4,5-Dihydro- 5-thioxo-1,3,4- thiadiazol-2- yl)amino]- carbonyl]amino]- 1-oxo-3- (pentafluoro- phenyl)propyl]- 4-(2-pyridinyl)- | | WO 97/40031 | |

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| Compound | Trade Name | Reference | Dosage |
|---|---|--|--------|
| piperazine | | | |
| hydroxamic acid derivatives of pyrrolidone-3- acetamide. | | WO 97/32846 | |
| alpha- arylsulfonamido- N-hydroxamic acid derivatives | | WO 98/17645 | |
| beta- Sulfonylhydrox- amic acids | | WO 98/13340 | |
| Hydroxamic acid derivatives | | US 5712300 | |
| | PNU-99533 (Pharmacia & UpJohn Inc.) | | |
| | PNU-143677 (Pharmacia & UpJohn Inc.) | | |
| | POL-641 (Poli- farma) | | |
| Peptidomimetic inhibitors | | WO 96/20,18. WO 96/29313. WO 98/08814. WO 98/08815. WO 98/08850. | |

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| Compound | Trade Name | Reference | Dosage |
|---|----------------------------|--|--|
| | | WO 98/08822. WO 98/08823. WO 98/08825. WO 98/08827. | |
| 2R)-N-hydroxycarboxamidemethyldecanoic acid amide of 1N-(carbomethoxymethyl) | (-)-caprolactam-(3S)-amine | WO 96/29313 | rheumatoid arthritis: female subject - 50 mg po for 2 yrs; male subject - 70 mg po daily for 5 yrs; corneal ulcer: male subject 0 10 mg in saline soln for 2 months, 2 times/day |
| 3-(N-[(N-Hydroxyaminocarbonyl)methyl]-N-isobutylaminocarbonyl)-2-(R)-isobutylpro- | | WO 96/20918 | |

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| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|--------|
| panoyl-L-phenylalanine amide | | | |
| N-hydroxy-phosphinic acid amides | | WO 98/08853 | |
| N'-arylsulfonyl derivatives of spirocyclic-N-hydroxycarbox-amides | | WO 98/08850 | |
| N'-arylsulfonyl derivatives of thiazepinone and azepinone-N-hydroxycarbox-amides | | WO 98/08827 | |
| Substituted piperazine derivatives | | WO 98/08825 | |
| N'-arylsulfonyl derivatives of pyrimidine, thiazepine and diazepine-N-hydroxycarbox-amides | | WO 98/08823 | |
| Substituted pyrrolidine derivatives | | WO 98/08815 | |

-74-

| Compound | Trade Name | Reference | Dosage |
|---|------------|--|--------|
| Substituted heterocycles | | WO 98/08814 | |
| Substituted 1,3-diheterocyclic derivatives | | WO 09/08822 | |
| substituted 5-amino-1,2,4-thiadiazole-2-thiones | | WO 98/25949 | |
| Hydroxamic acid derivatives which inhibit TNF production. | | WO 97/24117 | |
| 6-methoxy-1,2,3,4-tetrahydro-norharman-1-carboxylic acid | | WO 97/37658 | |
| | RS-130830 | Arthritis Rheum 1997 40 9 SUPPL. S128 | |
| Aralkyl MMP inhibitors (ex. N-(2R-carboxymethyl-5-(biphen-4-yl)pentanoyl)-L-t-butylglycine-N'-(pyridin-4- | | WO 96/16027 | |

-75-

| Compound | Trade Name | Reference | Dosage |
|--|--|-------------|--|
| yl) carboxamide) | | | |
| | Ro-32-3555 (Roche Holding AG) | | |
| | Ro-32-1278 (Roche Holding AG) | | |
| | Ro-32-1541 (Roche Holding AG) | | |
| | Ro-31-3790 (Roche Holding AG) | | Arthritic model rats: Protection of cartilage degradation following oral administrat ion; ED50 = 10 mg/kg po |
| (3R,11S)-N- hydroxy-5- methyl-3-(10- oxo-1,9- diazatricyclo- (11.6.1.014,19)e | | WO 95/04735 | |

-76-

| Compound | Trade Name | Reference | Dosage |
|--|------------|-------------|--------|
| icosa- 13(20),14(19),15 ,17-tetraen- 11- ylcarbamoyl)hexa namide and derivatives thereof | | | |
| Bridged indoles (Roche Holding AG) | | WO 96/23791 | |
| substituted phenylsulfonyl acetamide, propionamide and carboxamide compounds | | EP 780386 | |
| 5-(4'-biphenyl)- 5-[N-(4- nitrophenyl) piperazinyl] barbituric acid | | WO 97/23465 | |
| Malonic acid based matrix metalloproteinase inhibitors | | EP 716086 | |
| phenyl carboxamide derivatives | | WO 95/12603 | |
| Malonic acid based mmp | | EP 716086 | |

-77-

| Compound | Trade Name | Reference | Dosage |
|---|-------------------------|-----------|--------|
| inhibitors (specifically 2-(4-acetylamino-benzoyl)-4-methylpentanoic acid) | | | |
| Hydroxyl amine derivatives | Ro-31-4724; Ro-31-7467; | EP 236872 | |

The following individual patent references listed in Table No. 2 below, hereby individually incorporated by reference, describe various MMP inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 2. MMP inhibitors

| | | | |
|-------------|-------------|-------------|-------------|
| EP 189784 | US 4609667 | WO 98/25949 | WO 98/25580 |
| JP 10130257 | WO 98/17655 | WO 98/17645 | US 5760027 |
| US 5756545 | WO 98/22436 | WO 98/16514 | WO 98/16506 |
| WO 98/13340 | WO 98/16520 | WO 98/16503 | WO 98/12211 |
| WO 98/11908 | WO 98/15525 | WO 98/14424 | WO 98/09958 |
| WO 98/09957 | GB 23/18789 | WO 98/09940 | WO 98/09934 |
| JP 10045699 | WO 98/08853 | WO 98/06711 | WO 98/05635 |
| WO 98/07742 | WO 98/07697 | WO 98/03516 | WO 98/03166 |
| WO 98/03164 | GB 23/17182 | WO 98/05353 | WO 98/04572 |
| WO 98/04287 | WO 98/02578 | WO 97/48688 | WO 97/48685 |

| | | | |
|-------------|-------------|--------------|-------------|
| WO 97/49679 | WO 97/47599 | WO 97/43247 | WO 97/43240 |
| WO 97/43238 | EP 818443 | EP 818442 | WO 97/45402 |
| WO 97/40031 | WO 97/44315 | WO 97/38705 | US 5679700 |
| WO 97/43245 | WO 97/43239 | WO 97/43237 | JP 09227539 |
| WO 97/42168 | US 5686419 | WO 97/37974 | WO 97/36580 |
| WO 97/25981 | WO 97/24117 | US 5646316 | WO 97/23459 |
| WO 97/22587 | EP 780386 | DE 19548624 | WO 97/19068 |
| WO 97/19075 | WO 97/19050 | WO 97/18188 | WO 97/18194 |
| WO 97/18183 | WO 97/17088 | DE 19542189 | WO 97/15553 |
| WO 97/12902 | WO 97/12861 | WO 97/11936 | WO 97/11693 |
| WO 97/09066 | JP 09025293 | EP 75/8649 | WO 97/03966 |
| WO 97/03783 | EP 75/7984 | WO 97/02239 | WO 96/40745 |
| WO 96/40738 | WO 96/40737 | JP 08/311096 | WO 96/40204 |
| WO 96/40147 | WO 96/38434 | WO 96/35714 | WO 96/35712 |
| WO 96/35711 | WO 96/35687 | EP 74,3,070 | WO 96/33968 |
| WO 96/33165 | WO 96/33176 | WO 96/33172 | WO 96/33166 |
| WO 96/33161 | GB 23/00190 | WO 96/29313 | EP 73/6302 |
| WO 96/29307 | EP 733369 | WO 96/26223 | WO 96/27583 |
| WO 96/25156 | GB 22/98423 | WO 96/23791 | WO 96/23505 |
| GB 22/97324 | DE 19501032 | WO 96/20918 | US 5532265 |
| EP 719770 | WO 96/17838 | WO 96/16931 | WO 96/16648 |
| WO 96/16027 | EP 716086 | WO 96/15096 | JP 08104628 |
| WO 96/13523 | JP 08081443 | WO 96/11209 | EP 703239 |
| WO 96/06074 | WO 95/35276 | WO 96/00214 | WO 95/33731 |
| WO 95/33709 | WO 95/32944 | WO 95/29892 | WO 95/29689 |
| CA 21/16924 | WO 95/24921 | WO 95/24199 | WO 95/23790 |
| WO 95/22966 | GB 22/87023 | WO 95/19965 | WO 95/19961 |
| WO 95/19956 | WO 95/19957 | WO 95/13,289 | WO 95/13380 |
| WO 95/12603 | WO 95/09918 | WO 95/09841 | WO 95/09833 |
| WO 95/09620 | WO 95/08327 | GB 22/82598 | WO 95/07695 |

-79-

| | | | |
|-------------|-------------|-------------|-------------|
| WO 95/05478 | WO 95/04735 | WO 95/04033 | WO 95/02603 |
| WO 95/02045 | EP 626378 | WO 94/25435 | WO 94/25434 |
| WO 94/21612 | WO 94/24140 | WO 94/24140 | EP 622079 |
| WO 94/22309 | JP 06256209 | WO 94/21625 | FR 27/03053 |
| EP 606046 | WO 94/12169 | WO 94/11395 | GB 22/72441 |
| WO 94/07481 | WO 94/04190 | WO 94/00119 | GB 22/68934 |
| WO 94/02446 | EP 575844 | WO 93/24475 | WO 93/24449 |
| US 5270326 | US 5256657 | WO 93/20047 | WO 93/18794 |
| WO 93/14199 | WO 93/14096 | WO 93/13741 | WO 93/09090 |
| EP 53/2465 | EP 532156 | WO 93/00427 | WO 92/21360 |
| WO 92/09563 | WO 92/09556 | EP 48/9579 | EP 489577 |
| US 5114953 | EP 45/5818 | US 5010062 | AU 90/53158 |
| WO 97/19075 | US 7488460 | US 7494796 | US 7317407 |
| EP 277428 | EP 23/2027 | WO 96/15096 | WO 97/20824 |
| US 5837696 | | | |

The Marimastat used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 94/02,447.

5 The Bay-12-9566 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 96/15,096.

10 The AG-3340 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/20,824.

 The Metastat used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,837,696.

-80-

The D-2163 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/19,075.

More preferred zinc matrix metalloproteinase inhibitors include those described in the individual U.S. Patent applications, PCT publications and U.S. Patents listed below in Table No. 3, and are hereby individually incorporated by reference.

10 Table No. 3. More preferred zinc matrix metalloproteinase inhibitors

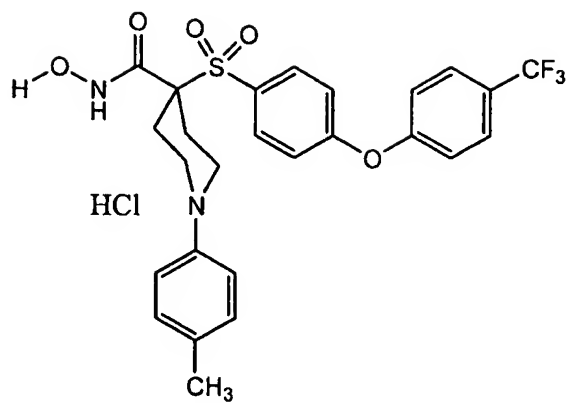
| |
|--|
| U.S. Patent Application Serial Number 97/12,873 |
| U.S. Patent Application Serial Number 97/12,874 |
| U.S. Patent Application Serial Number 98/04,299 |
| U.S. Patent Application Serial Number 98/04,273 |
| U.S. Patent Application Serial Number 98/04,297 |
| U.S. Patent Application Serial Number 98/04,300 |
| U.S. Patent Application Serial Number 60/119,181 |
| WO 94/02447 |
| WO 96/15096 |
| WO 97/20824 |
| WO 97/19075 |
| US 5837696 |

Even more preferred zinc matrix metalloproteinase inhibitors that may be used in the present invention include:

15

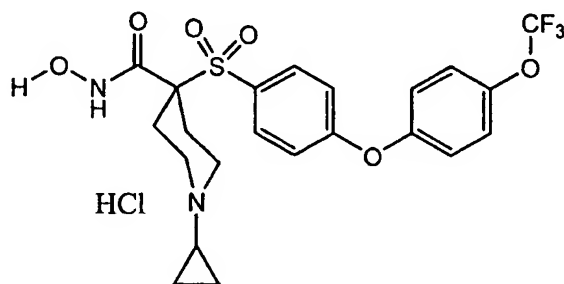
-81-

M1)



5 N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

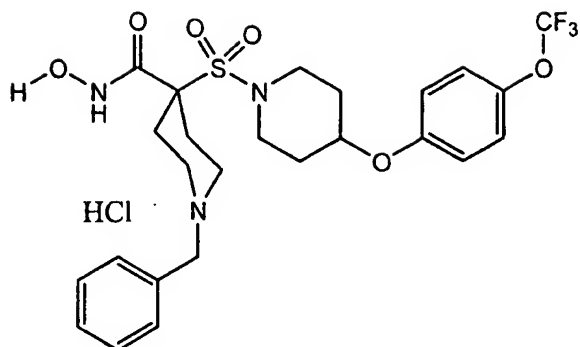
M2)



10 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

-82-

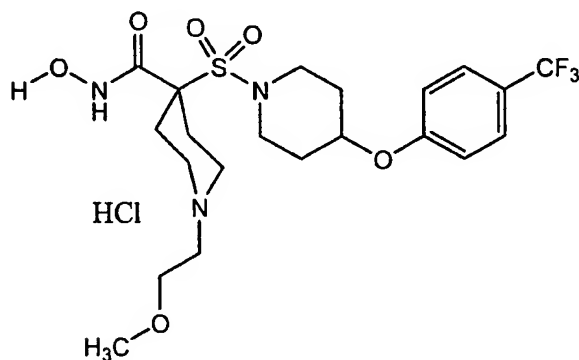
M3)



5

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M4)

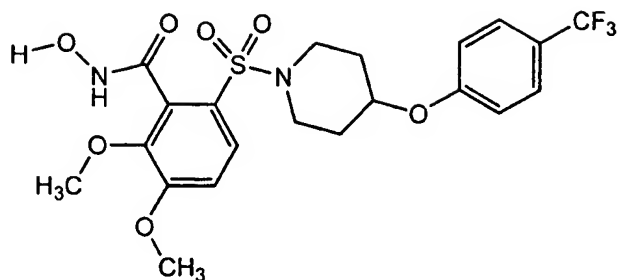


10

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

-83-

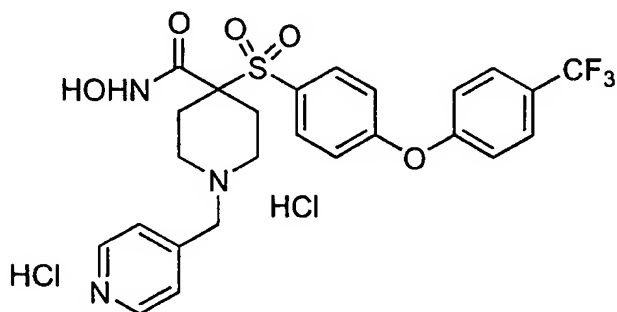
M5)



5

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidiny]sulfonyl]benzamide;

M6)

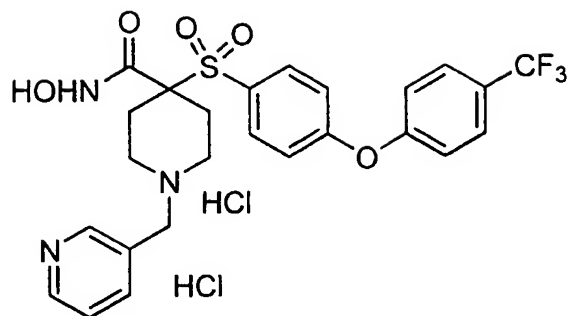


10

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

-84-

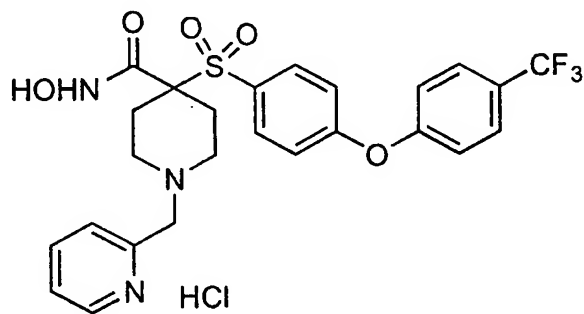
M7)



5

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M8)

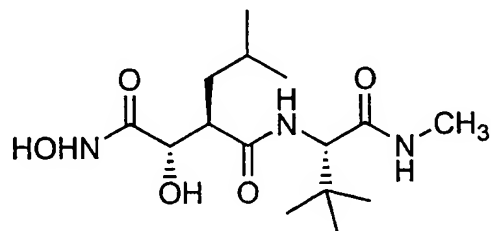


10

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

15

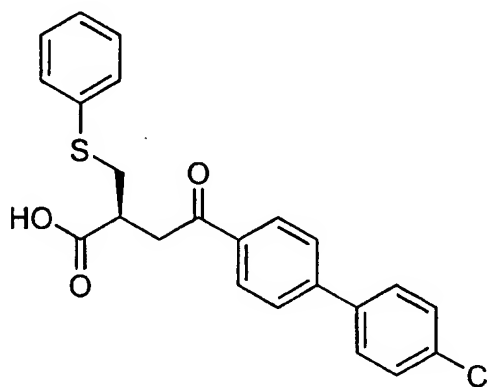
9)



-85-

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-);

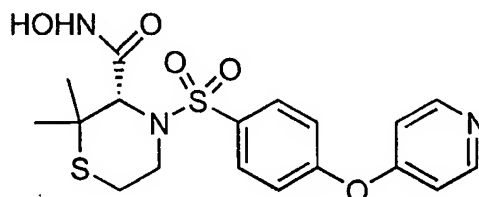
5 M10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]-4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid;

10

M11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide;

15

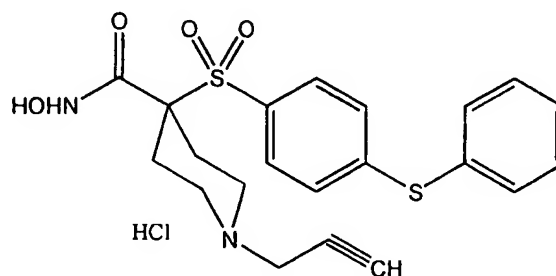
M12) CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline;

20

-86-

M13) Chiroscience D-2163, 2- [1S- ((2R,S)-
acetylmercapto- 5- phthalimido]pentanoyl- L-
leucyl)amino- 3- methylbutyl]imidazole;

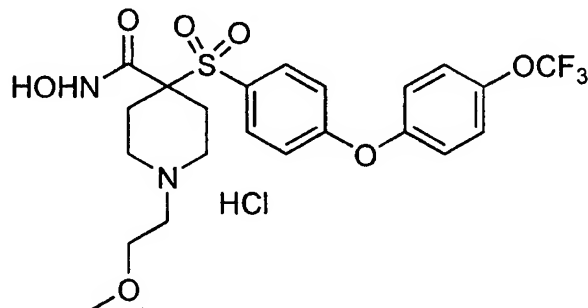
5 M14)



N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide
monohydrochloride;

10

M15)

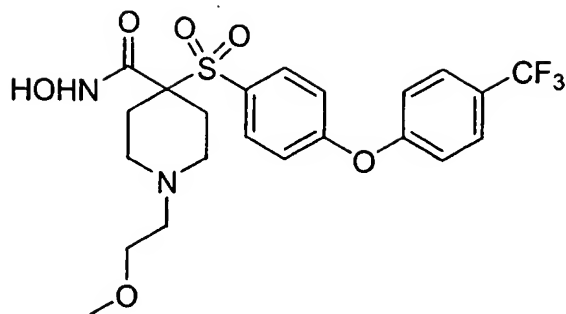


N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride;

15

-87-

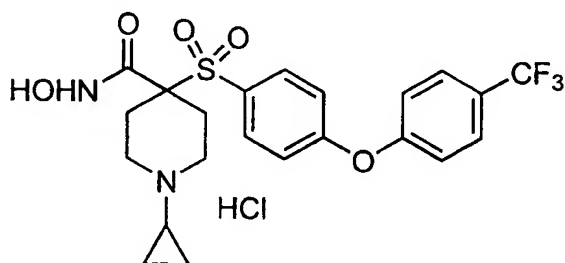
M16)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide;

5

M17)

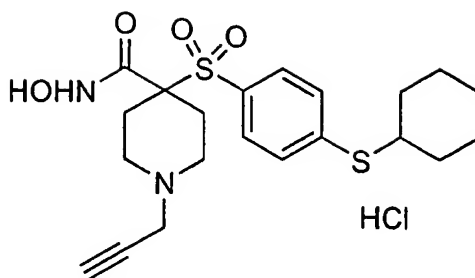


1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

10

-88-

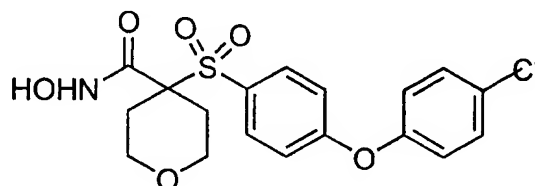
M18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-
hydroxy-1-(2-propynyl)-4-piperidinecarboxamide
monohydrochloride;

5

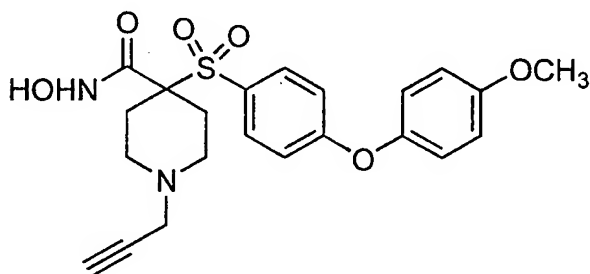
M19)



4-[[4-(4-
chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-
hydroxy-2H-pyran-4-carboxamide;

10

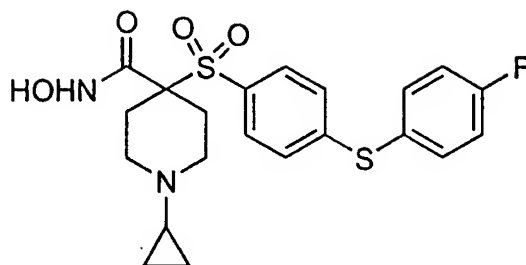
M20)



N-hydroxy-4-[[4-(4-
methoxyphenoxy)phenyl]sulfonyl]-1-(2-
propynyl)-4-piperidinecarboxamide;

15

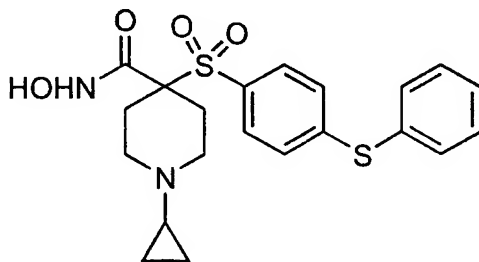
M21)



5

1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide;

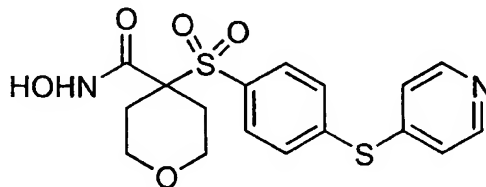
M22)



10

1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide;

M23)

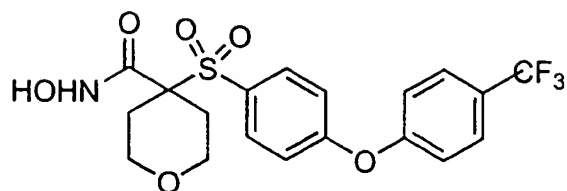


15

tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide;

-90-

M24)

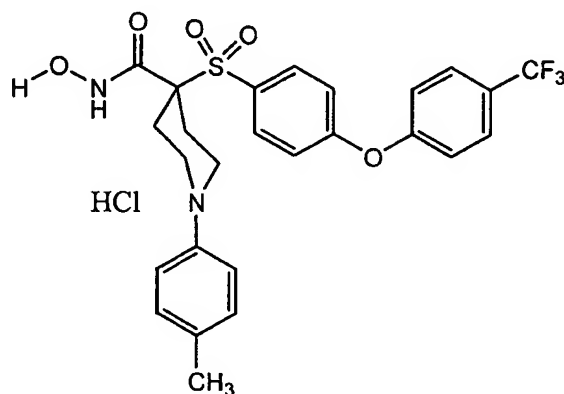


tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide.

5

Still more preferred MMP inhibitors include:

M1)

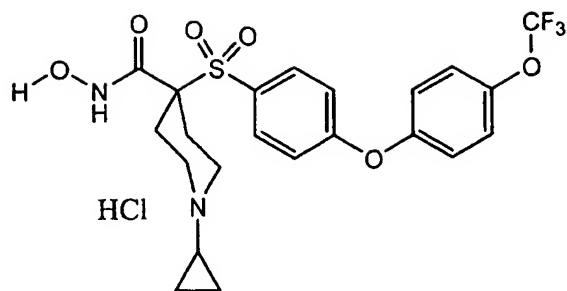


10

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

-91-

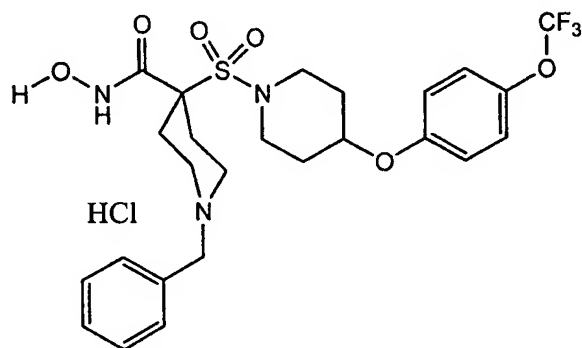
M2.)



5

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M3.)

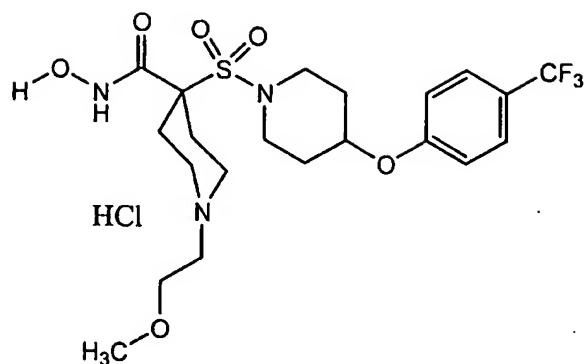


10

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

-92-

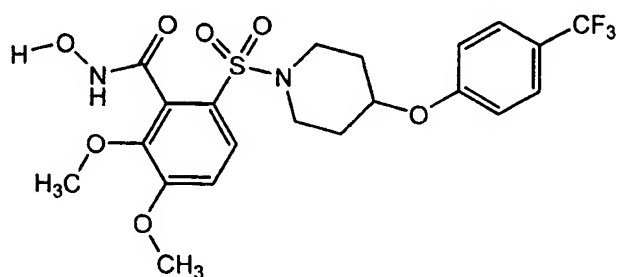
M4)



5

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M5)

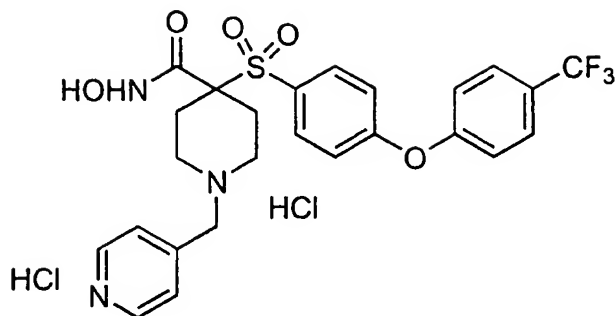


10

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide;

- 93 -

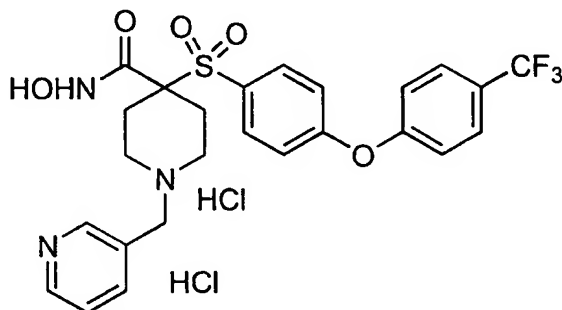
M6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

5

M7)

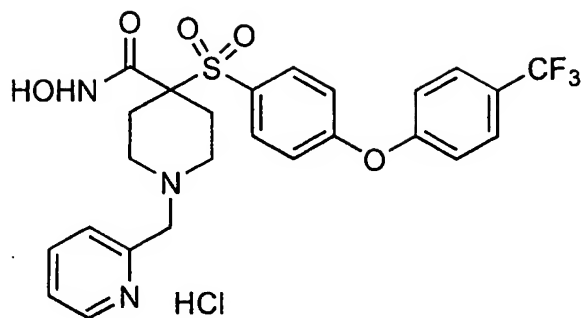


N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

10

-94-

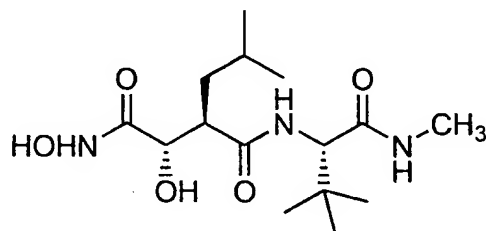
M8)



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M9)

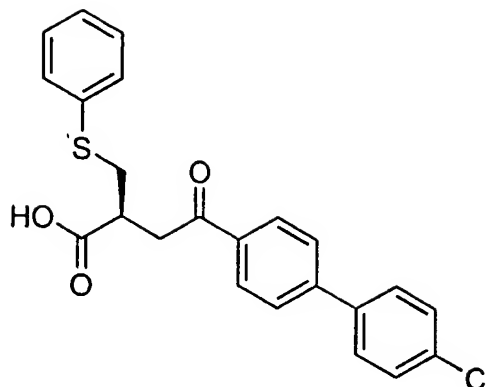


10

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-;

-95-

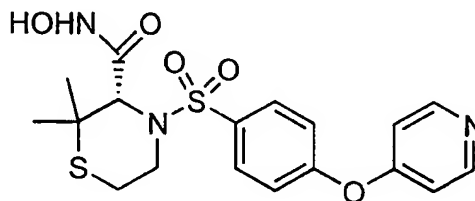
M10)



5

Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
 iphenyl]-4-yl)oxy]-2-
 [(phenylthio)methyl]butanoic acid;

M11)



10

Agouron Pharmaceuticals AG-3340, N-hydroxy-
 2,2- dimethyl- 4-[[4-(4-
 pyridinyloxy)phenyl]sulfonyl]- 3-
 thiomorpholinecarboxamide;

15

M12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
 6- demethyl-6-deoxy-4-
 dedimethylaminotetracycline;

20

M13) Chiroscience D-2163, 2- [1S- ((2R,S)-
 acetylmercapto- 5- phthalimido]pentanoyl- L-
 leucyl)amino- 3- methylbutyl]imidazole.

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The phrase "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" or "cyclooxygenase-II inhibitor" includes agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of
5 cyclooxygenase-1. Preferably, it includes compounds which have a cyclooxygenase-2 IC₅₀ of less than about 0.2 μ M, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at
10 least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC₅₀ of greater than about 1 μ M, and more preferably of greater than 10 μ M.

Studies indicate that prostaglandins synthesized by cyclooxygenases play a critical role in the initiation
15 and promotion of cancer. Moreover, COX-2 is overexpressed in neoplastic lesions of the colon, breast, lung, prostate, esophagus, pancreas, intestine, cervix, ovaries, urinary bladder, and head & neck. In several in vitro and animal models, COX-2 inhibitors
20 have inhibited tumor growth and metastasis.

In addition to cancers *per se*, COX-2 is also expressed in the angiogenic vasculature within and adjacent to hyperplastic and neoplastic lesions indicating that COX-2 plays a role in angiogenesis. In
25 both the mouse and rat, COX-2 inhibitors markedly inhibited bFGF-induced neovascularization. The utility of COX-2 inhibitors as chemopreventive, antiangiogenic and chemotherapeutic agents is described in the literature (Koki et al., Potential utility of COX-2
30 inhibitors in chemoprevention and chemotherapy. *Exp. Opin. Invest. Drugs* (1999) 8(10) pp. 1623-1638, hereby

-97-

incorporated by reference). Amplification and/or overexpression of HER-2/neu (ErbB2) occurs in 20-30% of human breast and ovarian cancers as well as in 5-15% of gastric and esophageal cancers and is associated with poor prognosis. Additionally, it has been recently discovered in vitro that COX-2 expression is upregulated in cells overexpressing the HER-2/neu oncogene. (Subbaramaiah et al., Increased expression of cyclooxygenase-2 in HER-2/neu-overexpressing breast cancer. Cancer Research (submitted 1999), hereby incorporated by reference). In this study, markedly increased levels of PGE₂ production, COX-2 protein and mRNA were detected in HER-2/neu transformed mammary epithelial cells compared to a non-transformed partner cell line. Products of COX-2 activity, i.e., prostaglandins, stimulate proliferation, increase invasiveness of malignant cells, and enhance the production of vascular endothelial growth factor, which promotes angiogenesis. Further, HER-2/neu induces the production of angiogenic factors such as vascular endothelial growth factor.

Consequently, the administration of a COX-2 inhibitor in combination with an anti HER-2/neu antibodies such as trastuzumab (Herceptin®) and other therapies directed at inhibiting HER-2/neu is contemplated to treat cancers in which HER-2/neu is overexpressed.

Also, it is contemplated that COX-2 levels are elevated in tumors with amplification and/or overexpression of other oncogenes including but not limited to *c-myc*, *N-myc*, *L-myc*, *K-ras*, *H-ras*, *N-ras*.

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Products of COX-2 activity stimulate cell proliferation, inhibit immune surveillance, increase invasiveness of malignant cells, and promote angiogenesis. Consequently, the administration of a COX-2 inhibitor in combination
5 with an agent or agents that inhibits or suppresses oncogenes is contemplated to prevent or treat cancers in which oncogenes are overexpressed.

Accordingly, there is a need for a method of treating or preventing cancer in a patient that
10 overexpresses COX-2 and/or an oncogene. Methods for the production of anti- ErbB2 antibodies are described in WO 99/31140.

Specific COX-2 inhibitors are useful for the treatment of cancer (WO98/16227) and in several animal
15 models reduce angiogenesis driven by various growth factors (WO98/22101). Anti-angiogenesis was achieved with a COX-2 inhibitor in rats implanted with bFGF, vascular endothelium growth factor (VEGF) or carrageenan, proteins with well-known angiogenic
20 properties. (Masferrer, et al., 89th Annual Meeting of the American Association for Cancer Research, March 1998.)

Pyrazoles can be prepared by methods described in WO 95/15,316. Pyrozoles can further be prepared by
25 methods described in WO 95/15315. Pyrozoles can also be prepared by methods described in WO 96/03385. Thiophene analogs can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932. Oxazoles can be prepared by
30 the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980. Isoxazoles

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can be prepared by the methods described in WO 96/25405. Imidazoles can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387. Cyclopentene cyclooxygenase-2 inhibitors
5 can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentane Cox-2 inhibitors is also described in WO 95/00501. Terphenyl compounds can be prepared by the methods described in WO 96/16934. Thiazole compounds can be prepared by the
10 methods described in WO 96/03,392. Pyridine compounds can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

Nonlimiting examples of COX-2 inhibitors that may
15 be used in the present invention are identified in Table No. 4 below.

Table No. 4. Cyclooxygenase-2 Inhibitors

| Compound | Trade/ Research Name | Reference | Dosage |
|---|-------------------------|---|--------|
| 1,5-Diphenyl-3-substituted pyrazoles | | WO 97/13755 | |
| | radicicol | WO 96/25928. Kwon et al (Cancer Res (1992) 52 6296) | |
| | GB-02283745 | | |
| | TP-72 | Cancer Res 1998 58 4 | |

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| Compound | Trade/ Research Name | Reference | Dosage |
|---|-------------------------|--------------|----------------|
| | | 717 -723 | |
| 1-(4-chlorobenzoyl)-3-[4-(4-fluorophenyl)thiazol-2-ylmethyl]-5-methoxy-2-methylindole | A-183827.0 | | |
| | GR-253035 | | |
| 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide | JTE-522 | JP 9052882 | |
| 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)-pyridine | | | |
| 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one | | | |
| | L-768277 | | |
| | L-783003 | | |
| | MK-966; VIOXX® | US 5968974 | 12.5-100 mg po |
| indomethacin- | | WO 96/374679 | 200 mg/kg/day |

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| Compound | Trade/ Research Name | Reference | Dosage |
|---|-------------------------|--|--------|
| derived indolalkanoic acid | | | |
| 1-Methylsulfonyl- 4-[1,1-dimethyl- 4-(4- fluorophenyl)cycl openta-2,4-dien- 3-yl]benzene | | WO 95/30656. WO 95/30652. WO 96/38418. WO 96/38442. | |
| 4,4-dimethyl-2- phenyl-3-[4- (methylsulfonyl)p henyl]cyclo- butenone | | | |
| 2-(4- methoxyphenyl)-4- methyl-1-(4- sulfamoylphenyl)- pyrrole | | EP 799823 | |
| N-[5-(4- fluoro)phenoxy]th iophene-2- methanesulfon- amide | RWJ-63556 | | |
| 5(E)-(3,5-di- tert-butyl-4- hydroxy)benzylide ne-2-ethyl-1,2- isothiazolidine- | S-2474 | EP 595546 | |

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| Compound | Trade/ Research Name | Reference | Dosage |
|---|-------------------------|-------------|--------------|
| 1,1-dioxide | | | |
| 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one | T-614 | DE 38/34204 | |
| Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)- | celecoxib | US 5466823 | |
| CS 502 | (Sankyo) | | |
| MK 633 | (Merck) | | |
| | meloxicam | US 4233299 | 15-30 mg/day |
| | nimesulide | US 3840597 | |

The following references listed in Table No. 5 below, hereby individually incorporated by reference, describe various COX-2 inhibitors suitable for use in the present invention described herein, and processes

5 for their manufacture.

Table No. 5 COX-2 inhibitors

| | | | |
|-------------|-------------|-------------|-------------|
| WO 99/30721 | WO 99/30729 | US 5760068 | WO 98/15528 |
| WO 99/25695 | WO 99/24404 | WO 99/23087 | FR 27/71005 |
| EP 921119 | FR 27/70131 | WO 99/18960 | WO 99/15505 |
| WO 99/15503 | WO 99/14205 | WO 99/14195 | WO 99/14194 |
| WO 99/13799 | GB 23/30833 | US 5859036 | WO 99/12930 |
| WO 99/11605 | WO 99/10332 | WO 99/10331 | WO 99/09988 |

| | | | |
|--------------|-------------|--------------|-------------|
| US 5869524 | WO 99/05104 | US 5859257 | WO 98/47890 |
| WO 98/47871 | US 5830911 | US 5824699 | WO 98/45294 |
| WO 98/43966 | WO 98/41511 | WO 98/41864 | WO 98/41516 |
| WO 98/37235 | EP 86/3134 | JP 10/175861 | US 5776967 |
| WO 98/29382 | WO 98/25896 | ZA 97/04806 | EP 84/6,689 |
| WO 98/21195 | GB 23/19772 | WO 98/11080 | WO 98/06715 |
| WO 98/06708 | WO 98/07425 | WO 98/04527 | WO 98/03484 |
| FR 27/51966 | WO 97/38986 | WO 97/46524 | WO 97/44027 |
| WO 97/34882 | US 5681842 | WO 97/37984 | US 5686460 |
| WO 97/36863 | WO 97/40012 | WO 97/36497 | WO 97/29776 |
| WO 97/29775 | WO 97/29774 | WO 97/28121 | WO 97/28120 |
| WO 97/27181 | WO 95/11883 | WO 97/14691 | WO 97/13755 |
| WO 97/13755 | CA 21/80624 | WO 97/11701 | WO 96/41645 |
| WO 96/41626 | WO 96/41625 | WO 96/38418 | WO 96/37467 |
| WO 96/37469 | WO 96/36623 | WO 96/36617 | WO 96/31509 |
| WO 96/25405 | WO 96/24584 | WO 96/23786 | WO 96/19469 |
| WO 96/16934 | WO 96/13483 | WO 96/03385 | US 5510368 |
| WO 96/09304 | WO 96/06840 | WO 96/06840 | WO 96/03387 |
| WO 95/21817 | GB 22/83745 | WO 94/27980 | WO 94/26731 |
| WO 94/20480 | WO 94/13635 | FR 27/70,131 | US 5859036 |
| WO 99/01131 | WO 99/01455 | WO 99/01452 | WO 99/01130 |
| WO 98/57966 | WO 98/53814 | WO 98/53818 | WO 98/53817 |
| WO 98/47890 | US 5830911 | US 5776967 | WO 98/22101 |
| DE 19/753463 | WO 98/21195 | WO 98/16227 | US 5733909 |
| WO 98/05639 | WO 97/44028 | WO 97/44027 | WO 97/40012 |
| WO 97/38986 | US 5677318 | WO 97/34882 | WO 97/16435 |
| WO 97/03678 | WO 97/03667 | WO 96/36623 | WO 96/31509 |
| WO 96/25928 | WO 96/06840 | WO 96/21667 | WO 96/19469 |
| US 5510368 | WO 96/09304 | GB 22/83745 | WO 96/03392 |
| WO 94/25431 | WO 94/20480 | WO 94/13635 | JP 09052882 |

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| | | | |
|-------------|-------------|-------------|-------------|
| GB 22/94879 | WO 95/15316 | WO 95/15315 | WO 96/03388 |
| WO 96/24585 | US 5344991 | WO 95/00501 | US 5968974 |
| US 5945539 | US 5994381 | | |

The celecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

5 The valdecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

 The parecoxib used in the therapeutic combinations of the present invention can be prepared in the manner
10 set forth in U.S. Patent No. 5,932,598.

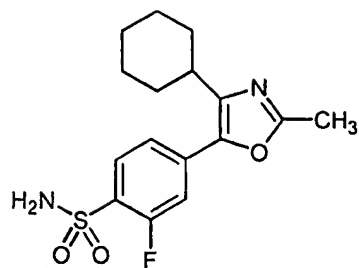
 The rofecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,968,974.

 The Japan Tobacco JTE-522 used in the therapeutic
15 combinations of the present invention can be prepared in the manner set forth in JP 90/52,882.

 Preferred COX-2 inhibitors that may be used in the present invention include, but are not limited to:

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C1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-
2-fluorobenzenesulfonamide;

5

C2)

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-
pyridinyl)pyridine;

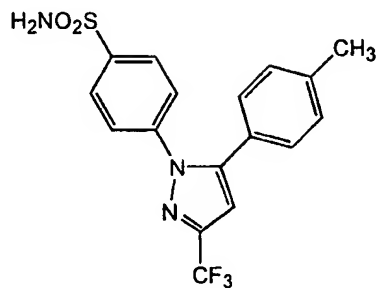
10

C3)

2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-
cyclopenten-1-one;

15

C4)

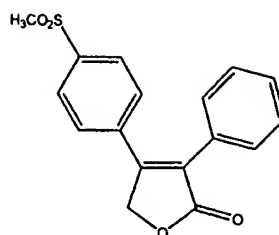


4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-
pyrazol-1-yl]-benzenesulfonamide;

20

-106-

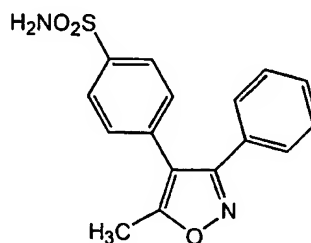
C5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone;

5

C6)



4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

10

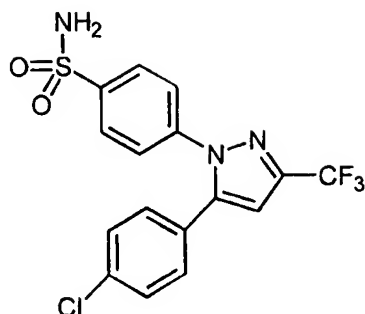
C7)

N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;

15

-107-

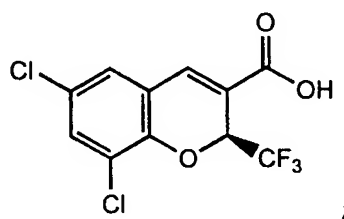
C8)



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;

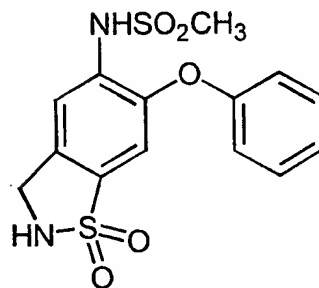
5

C9)



;

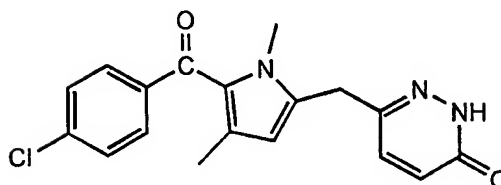
C10)



;

10

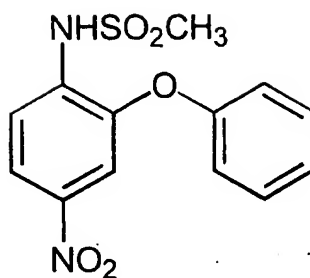
C11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;

-108-

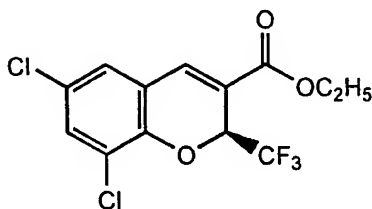
C12)



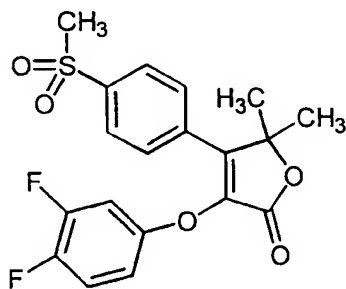
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide;

5

C13)



C14)

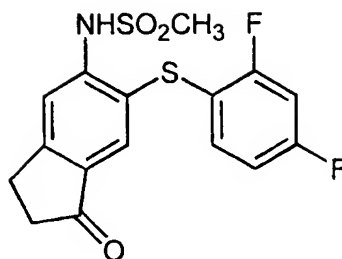


10

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;

-109-

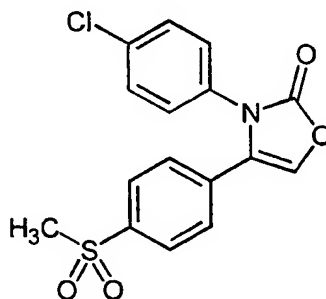
C15)



N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;

5

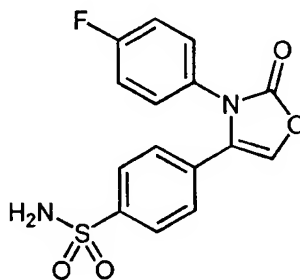
C16)



3-(4-chlorophenyl)-4-[4-(methanesulfonyl)phenyl]-2(3H)-oxazolone;

10

C17)

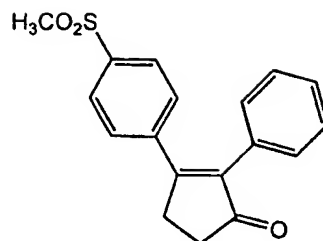


4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;

15

-110-

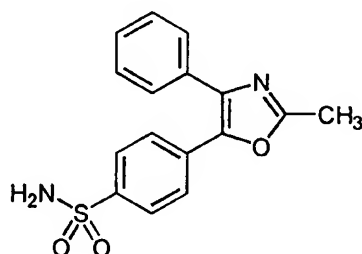
C18)



3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one;

5

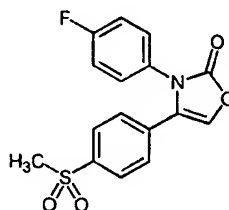
C19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide;

10

C20)

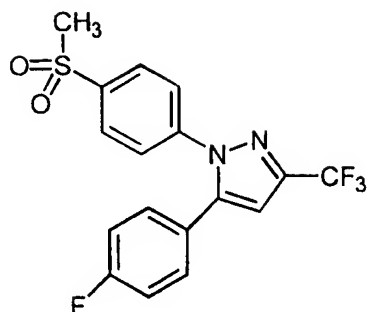


3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;

15

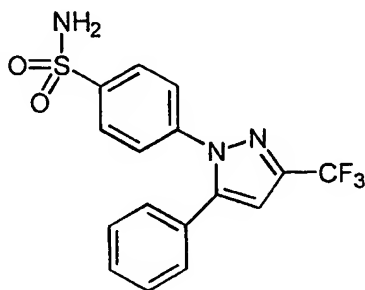
-111-

C21)



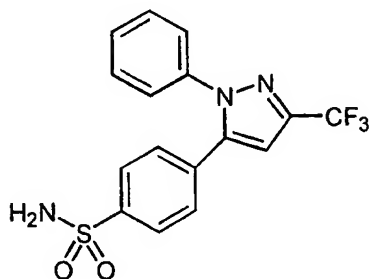
5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-
1H-pyrazole;

C22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

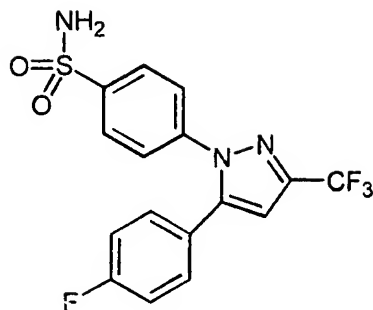
C23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;

-112-

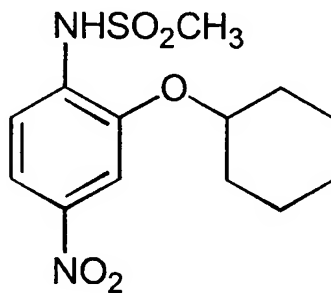
C24)



4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

5

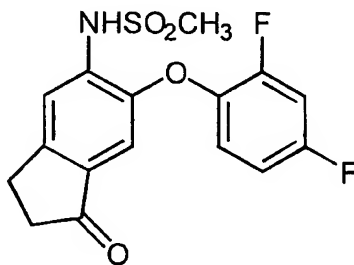
C25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide;

10

C26)

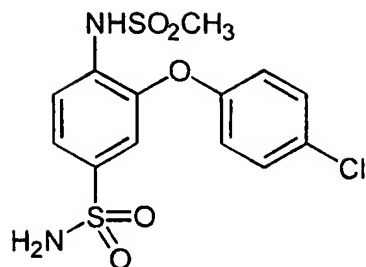


N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;

15

-113-

C27)

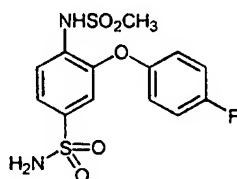


3-(4-chlorophenoxy)-4-

5

[(methylsulfonyl)amino]benzenesulfonamide;

C28)

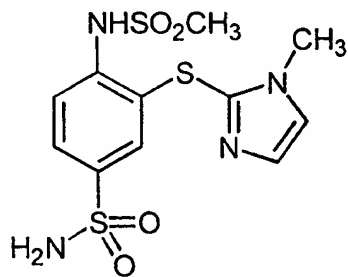


3-(4-fluorophenoxy)-4-

10

[(methylsulfonyl)amino]benzenesulfonamide;

C29)



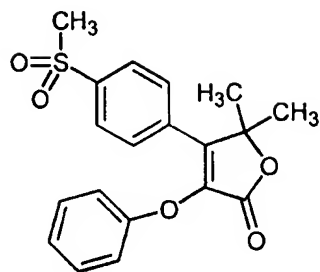
3-[(1-methyl-1H-imidazol-2-yl)thio]-4

15

[(methylsulfonyl) amino]benzenesulfonamide;

-114-

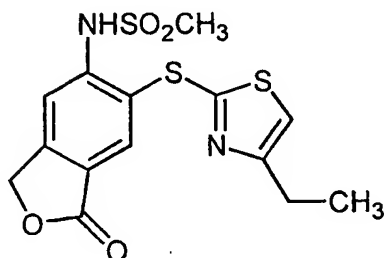
C30)



5

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone;

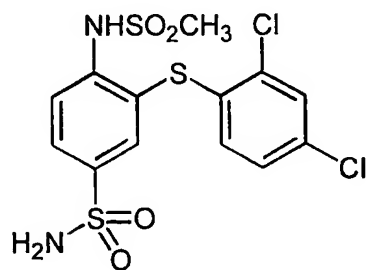
C31)



10

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide;

C32)

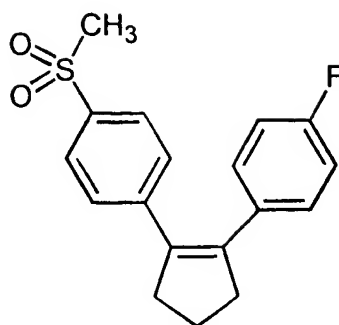


15

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide;

-115-

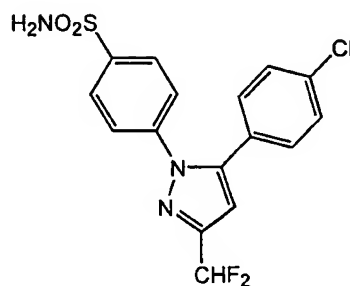
C33)



1-fluoro-4-[2-[4-(
(methylsulfonyl)phenyl]cyclopenten-1-
yl]benzene;

5

C34)

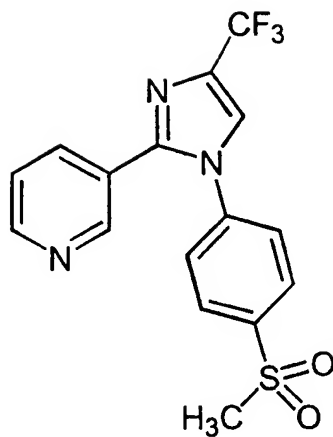


4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-
pyrazol-1-yl]benzenesulfonamide;

10

-116-

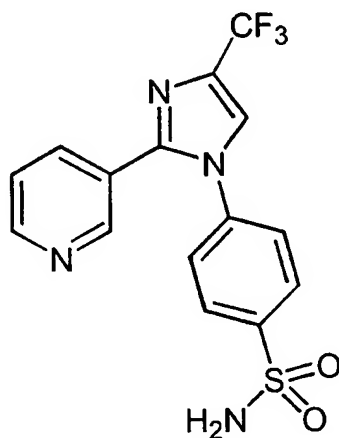
C35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

5

C36)

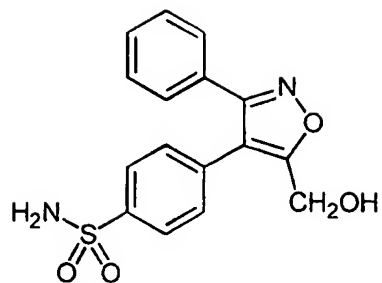


4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

10

-117-

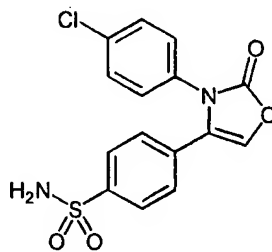
C37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

5

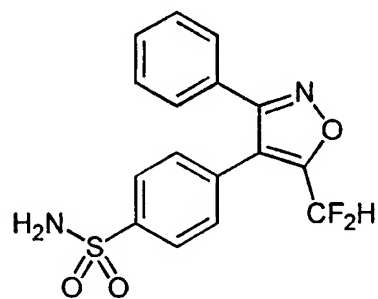
C38)



4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;

10

C39)

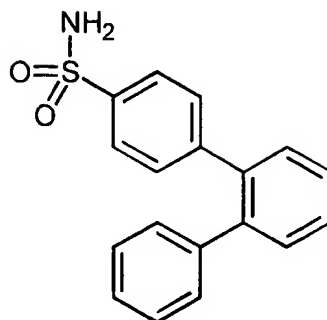


4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;

15

-118-

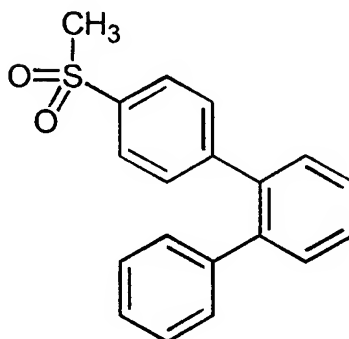
C40)



[1,1':2',1''-terphenyl]-4-sulfonamide;

5

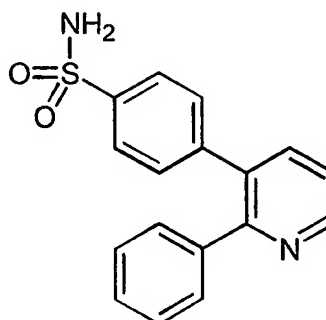
C41)



4-(methylsulfonyl)-1,1',2],1''-terphenyl;

10

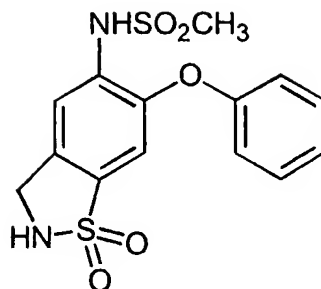
C42)



4-(2-phenyl-3-pyridinyl)benzenesulfonamide;

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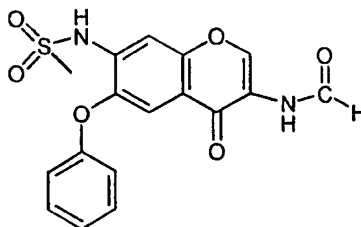
C43)



N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide; and

5

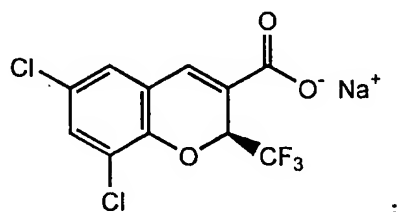
C44)



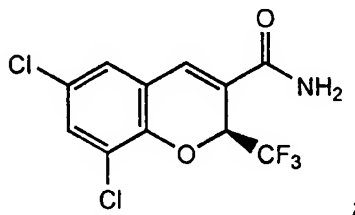
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide;

10

45)

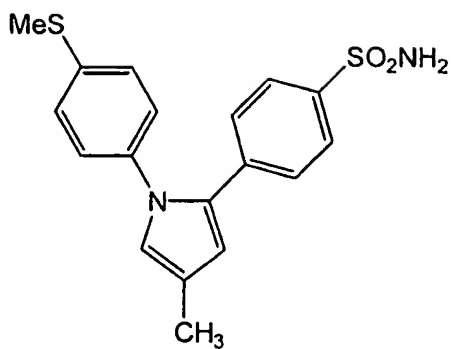


46)

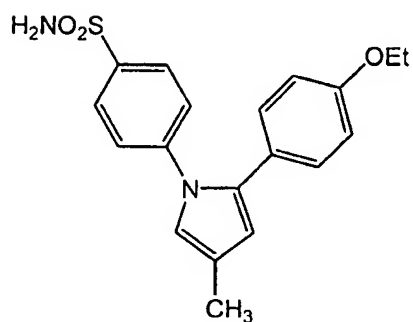


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47)



48)

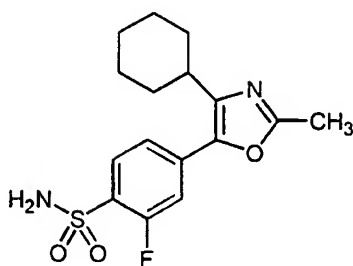


5

More preferred COX-2 inhibitors that may be used in the present invention are selected from the group consisting of:

10

C1).



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide;

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C2)

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine;

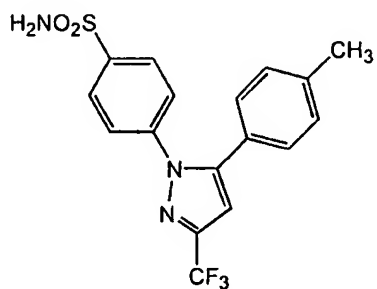
5

C3)

2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;

10

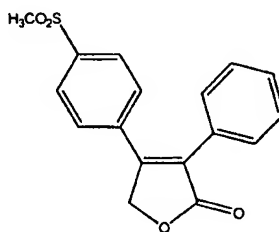
C4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;

15

C5)

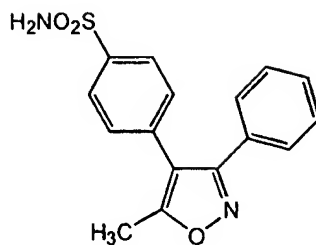


rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone;

20

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C6)



4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

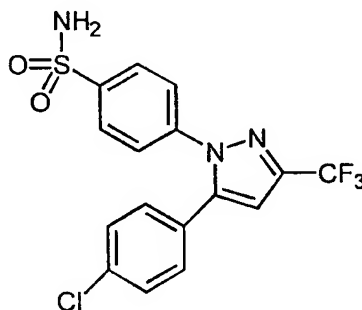
5

C7)

N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;

10

C8)



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;

15

Still more preferably, the COX-2 inhibitors that may be used in the present invention include, but are not limited to celecoxib, valdecoxib, parecoxib, rofecoxib, and Japan Tobacco JTE-522.

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Dosage of MMP and COX-2 Inhibitors

Dosage levels of MMP and COX-2 inhibitors on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. The amount of active ingredient that may be combined with other anticancer agents to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with

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the concentrations found to be effective in vitro. Thus, where an compound is found to demonstrate in vitro activity at, e.g., 10 μ M, one will desire to administer an amount of the drug that is effective to provide about
5 a 10 μ M concentration in vivo. Determination of these parameters are well within the skill of the art.

These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard
10 textbooks.

Administration Regimen

Any effective treatment regimen can be utilized and readily determined and repeated as necessary to effect
15 treatment. In clinical practice, the compositions containing a MMP and COX-2 inhibitor alone or in combination with other therapeutic agents are administered in specific cycles until a response is obtained.

20 For patients who initially present without advanced or metastatic cancer, a MMP and COX-2 inhibitor in combination with radiation therapy, is used as a continuous post-treatment therapy in patients at risk for recurrence or metastasis (for example, in
25 adenocarcinoma of the prostate, risk for metastasis is based upon high PSA, high Gleason's score, locally extensive disease, and/or pathological evidence of tumor invasion in the surgical specimen). The goal in these patients is to inhibit the growth of potentially
30 metastatic cells from the primary tumor during surgery

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and inhibit the growth of tumor cells from undetectable residual primary tumor.

For patients who initially present with advanced or metastatic cancer, a MMP and COX-2 inhibitor in
5 combination with radiation therapy of the present invention is used as a continuous supplement to, or possible replacement for hormonal ablation. The goal in these patients is to slow or prevent tumor cell growth from both the untreated primary tumor and from the
10 existing metastatic lesions.

Also included in the combination of the invention are the isomeric forms, prodrugs and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable
15 salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic,
20 mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

25 Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth
30 metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of

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aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-
5 dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present
10 invention.

A MMP or COX-2 inhibitor of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or
15 topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or
20 iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical
25 Sciences, Mack Publishing Co., Easton, Pennsylvania 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

30 Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be

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formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated

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aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated MMP or COX-2 inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions,

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solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and
5 sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

10 The phrase "antineoplastic agents" includes agents that exert antineoplastic effects, i.e., prevent the development, maturation, or spread of neoplastic cells, directly on the tumor cell, e.g., by cytostatic or cytocidal effects, and not indirectly through mechanisms
15 such as biological response modification. There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be included in the present invention for treatment of neoplasia by
20 combination drug chemotherapy. For convenience of discussion, antineoplastic agents are classified into the following classes, subtypes and species:

ACE inhibitors,
alkylating agents,
25 angiogenesis inhibitors,
angiostatin,
anthracyclines/DNA intercalators,
anti-cancer antibiotics or antibiotic-type agents,
antimetabolites,
30 antimetastatic compounds,
asparaginases,

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bisphosphonates,
cGMP phosphodiesterase inhibitors,
calcium carbonate,
cyclooxygenase-2 inhibitors
5 DHA derivatives,
DNA topoisomerase,
endostatin,
epipodophylotoxins,
genistein,
10 hormonal anticancer agents,
hydrophilic bile acids (URSO),
immunomodulators or immunological agents,
integrin antagonists
interferon antagonists or agents,
15 MMP inhibitors,
miscellaneous antineoplastic agents,
monoclonal antibodies,
nitrosoureas,
NSAIDs,
20 ornithine decarboxylase inhibitors,
pBATTs,
radio/chemo sensitizers/protectors,
retinoids
selective inhibitors of proliferation and migration
25 of endothelial cells,
selenium,
stromelysin inhibitors,
taxanes,
vaccines, and
30 vinca alkaloids.

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The major categories that some preferred antineoplastic agents fall into include antimetabolite agents, alkylating agents, antibiotic-type agents, hormonal anticancer agents, immunological agents, 5 interferon-type agents, and a category of miscellaneous antineoplastic agents. Some antineoplastic agents operate through multiple or unknown mechanisms and can thus be classified into more than one category.

A first family of antineoplastic agents which may be 10 used in combination with the present invention consists of antimetabolite-type antineoplastic agents. Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic 15 acids. Suitable antimetabolite antineoplastic agents that may be used in the present invention include, but are not limited to acanthifolic acid, aminothiadiaazole, anastrozole, bicalutamide, brequinar sodium, capecitabine, carmofur, Ciba-Geigy CGP-30694, cladribine, cyclopentyl 20 cytosine, cytarabine phosphate stearate, cytarabine conjugates, cytarabine ocfosphate, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, finasteride, floxuridine, 25 fludarabine phosphate, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, fluorouracil (5-FU), 5-FU-fibrinogen, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, nafarelin, norspermidine, nolvadex, NCI NSC-127716, NCI 30 NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical

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PL-AC, stearate; Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, toremifene, and uricytin.

- 5 Preferred antimetabolite agents that may be used in the present invention include, but are not limited to, those identified in Table No. 6, below.

Table No. 6. Antimetabolite agents

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|---|-------------------|------------|----------------------------|
| 1,3-Benzenediacetonitrile, alpha, alpha, alpha', alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)- | anastrozole ; ARIMIDEX® | Zeneca | EP 296749 | 1-mg/day |
| Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (+/-)- | bicalutamide; CASODEX® | Zeneca | EP 100172 | 50 mg once daily |
| | capecitabine | Roche | US 5472949 | |
| Adenosine, 2-chloro-2'-deoxy-; 2-chloro-2'-deoxy-(beta)-D-adenosine) | cladribine; 2-CdA; LEUSTAT; LEUSTA-TIN®; LEUSTA-TIN® injection; LEUSTATINE®; RWJ- | Johnson & Johnson | EP 173059 | 0.09 mg/kg/day for 7 days. |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|--|--|------------|---|
| | 26251; | | | |
| 2 (1H) - Pyrimidinone, 4-amino-1-[5- O- [hydroxy(octad ecyloxy)phosph inyl]-beta-D- arabinofuranos yl]-, monosodium salt | cytarabine ocfosfate; ara CMP stearyl ester; C- 18-PCA; cytarabine phosphate stearate; Starasid; YNK-01; CYTOSAR-U® | Yamasa Corp | EP 239015 | 100 - 300 mg/day for 2 weeks |
| 4-Azaandrost- 1-ene-17- carboxamide, N-(1,1- dimethylethyl) -3-oxo- , (5alpha,17beta)- | finasteride ; PROPECIA® | Merck & Co | EP 155096 | |
| | fluorouraci l (5-FU) | | US 4336381 | |
| Fludarabine phosphate. 9H-Purin-6- amine, 2- fluoro-9-(5-O- phosphono- beta- D- arabinofuranos yl) | fludarabine phosphate; 2-F-araAMP; Fludara; Fludara iv; Fludara Oral; NSC- 312887; SH- 573; SH- 584; SH- 586; | Southern Research Institute ; Berlex | US 4357324 | 25 mg/m ² /d IV over a period of approx- imately 30 minutes daily for 5 con- secutive days, commenced every 28 days. |
| | gemcitabi ne | Eli Lilly | US 4526988 | |
| N-(4-((2,4- diamino- 6- pteridiny)met hyl)methylamin o)benzoyl)-L- | methotrexat e iv, Hyal; HA + methotrexat e, Hyal; | Hyal Pharma- ceutical; American Home | US 2512572 | tropho- blastic diseases: 15 to 30 mg/d |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|---|----------------------|------------|--|
| glutamic acid | methotrexate iv, HIT Technolog; | Products; Lederle | | orally or intra- muscularly in a five- day course (repeated 3 to 5 times as needed) |
| Luteinizing hormone- releasing factor (pig), 6-[3-(2- naphthalenyl)- D-alanine]- | nafarelin | Roche | EP 21234 | |
| | pentostatin ; CI-825; DCF; deoxycoform ycin; Nipent; NSC-218321; Oncopent; | Warner- Lambert | US 3923785 | |
| Ethanamine, 2- [4-(4-chloro- 1,2-diphenyl- 1- butenyl)phenoxy]-N,N- dimethyl-, (Z)- | toremifene; FARESTON® | Orion Pharma | EP 95875 | 60 mg/d |

A second family of antineoplastic agents which may be used in combination with the present invention consists of alkylating-type antineoplastic agents. The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A

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disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue. Suitable alkylating-type antineoplastic agents that may be used in the present invention include, but are not limited to, Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine (BiCNU), Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, dacarbazine, Degussa D-19-384, Sumimoto DACHP(Myrr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, etoposide phosphate, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, mycophenolate, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, thiotepa, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

Preferred alkylating agents that may be used in the present invention include, but are not limited to, those identified in Table No. 7, below.

Table No. 7. Alkylating agents

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---------------------------|------------------------------|---------------------------------|---|
| Platinum, diammine[1,1-cyclobutanedicarboxylato(2-)]-, (SP-4-2)- | carboplatin; PARAPLATIN ® | Johnson Matthey | US 4657927. US 4140707. | 360 mg/m ² (squared) I.V. on day 1 every 4 weeks. |
| Carmustine, 1,3-bis (2-chloroethyl)-1-nitrosourea | BiCNU® | Ben Venue Laboratories, Inc. | JAMA 1985; 253 (11): 1590-1592. | Preferred: 150 to 200 mg/ m ² every 6 wks. |
| | etoposide phosphate | Bristol-Myers Squibb | US 4564675 | |
| | thiotepa | | | |
| Platinum, diamminedichloro-, (SP-4-2)- | cisplatin; PLATINOL-AQ | Bristol-Myers Squibb | US 4177263 | |
| dacarbazine | DTIC Dome | Bayer | | 2 to 4.5mg/kg/day for 10 days; 250mg/ square meter body surface/ day I.V. for 5 days every 3 weeks |
| ifosfamide | IFEX | Bristol-Meyers Squibb | | 4-5 g/m ² (square) single bolus dose, or 1.2-2 g/m ² (square) I.V. over 5 days. |
| | cyclophosphamide | | US 4537883 | |
| cis- | Platinol | Bristol- | | 20 mg/M ² |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|-------------------------|-------------------------|--------------|-----------|-----------------------------|
| diaminedichloroplatinum | Cisplatin | Myers Squibb | | IV daily for a 5 day cycle. |

A third family of antineoplastic agents which may be used in combination with the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents that may be used in the present invention include, but are not limited to Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, caliche mycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313,

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Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

Preferred antibiotic anticancer agents that may be used in the present invention include, but are not limited to, those agents identified in Table No. 8, below.

Table No. 8. Antibiotic anticancer agents

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|----------------------------|--|-------------|---|
| 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester, (E)- | mycophenolate mofetil | Roche | WO 91/19498 | 1 to 3 gm/d |
| | mitoxantrone | | US 4310666 | |
| | doxorubicin | | US 3590028 | |
| Mitomycin and/or mitomycin-C | Mutamycin | Bristol-Myers Squibb Oncology/Immunology | | After full hematological recovery from any previous |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|----------|----------------------------|---------|-----------|--|
| | | | | chemo- therapy: 20 mg/m ² intra- venously as a single dose via a function- ing intra- venous catheter. |

A fourth family of antineoplastic agents which may be used in combination with the present invention consists of synthetic nucleosides. Several synthetic nucleosides have been identified that exhibit anticancer activity. A well known nucleoside derivative with strong anticancer activity is 5-fluorouracil (5-FU). 5-Fluorouracil has been used clinically in the treatment of malignant tumors, including, for example, carcinomas, sarcomas, skin cancer, cancer of the digestive organs, and breast cancer. 5-Fluorouracil, however, causes serious adverse reactions such as nausea, alopecia, diarrhea, stomatitis, leukocytic thrombocytopenia, anorexia, pigmentation, and edema. Derivatives of 5-fluorouracil with anti-cancer activity have been described in U.S. Pat. No. 4,336,381. Further 5-FU derivatives have been described in the following patents listed in Table No. 9, hereby individually incorporated by reference herein.

Table No. 9. 5-Fu derivatives

| | | |
|-------------|-------------|-------------|
| JP 50-50383 | JP 50-50384 | JP 50-64281 |
|-------------|-------------|-------------|

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| | | |
|--------------|-------------|--|
| JP 51-146482 | JP 53-84981 | |
|--------------|-------------|--|

U.S. Pat. No. 4,000,137 discloses that the peroxidate oxidation product of inosine, adenosine, or cytidine with methanol or ethanol has activity against lymphocytic leukemia. Cytosine arabinoside (also referred to as Cytarabin, araC, and Cytosar) is a nucleoside analog of deoxycytidine that was first synthesized in 1950 and introduced into clinical medicine in 1963. It is currently an important drug in the treatment of acute myeloid leukemia. It is also active against acute lymphocytic leukemia, and to a lesser extent, is useful in chronic myelocytic leukemia and non-Hodgkin's lymphoma. The primary action of araC is inhibition of nuclear DNA synthesis. Handschumacher, R. and Cheng, Y., "Purine and Pyrimidine Antimetabolites", Cancer Medicine, Chapter XV-1, 3rd Edition, Edited by J. Holland, et al., Lea and Febigol, publishers.

5-Azacytidine is a cytidine analog that is primarily used in the treatment of acute myelocytic leukemia and myelodysplastic syndrome.

2-Fluoroadenosine-5'-phosphate (Fludara, also referred to as FaraA) is one of the most active agents in the treatment of chronic lymphocytic leukemia. The compound acts by inhibiting DNA synthesis. Treatment of cells with F-araA is associated with the accumulation of cells at the G1/S phase boundary and in S phase; thus, it is a cell cycle S phase-specific drug. InCorp of the active metabolite, F-araATP, retards DNA chain elongation. F-araA is also a potent inhibitor of

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ribonucleotide reductase, the key enzyme responsible for the formation of dATP. 2-Chlorodeoxyadenosine is useful in the treatment of low grade B-cell neoplasms such as chronic lymphocytic leukemia, non-Hodgkins' lymphoma, and hairy-cell leukemia. The spectrum of activity is similar to that of Fludara. The compound inhibits DNA synthesis in growing cells and inhibits DNA repair in resting cells.

A fifth family of antineoplastic agents which may be used in combination with the present invention consists of hormonal agents. Suitable hormonal-type antineoplastic agents that may be used in the present invention include, but are not limited to Abarelix; Abbott A-84861; Abiraterone acetate; Aminoglutethimide; anastrozole; Asta Medica AN-207; Antide; Chugai AG-041R; Avorelin; aseranox; Sensus B2036-PEG; Bicalutamide; buserelin; BTG CB-7598; BTG CB-7630; Casodex; cetrolin; clastroban; clodronate disodium; Cosudex; Rotta Research CR-1505; cytradren; crinone; deslorelin; droloxifene; dutasteride; Elimina; Laval University EM-800; Laval University EM-652; epitiostanol; epristeride; Mediolanum EP-23904; EntreMed 2-ME; exemestane; fadrozole; finasteride; flutamide; formestane; Pharmacia & Upjohn FCE-24304; ganirelix; goserelin; Shire gonadorelin agonist; Glaxo Wellcome GW-5638; Hoechst Marion Roussel Hoe-766; NCI hCG; idoxifene; isocordoin; Zeneca ICI-182780; Zeneca ICI-118630; Tulane University J015X; Schering Ag J96; ketanserin; lanreotide; Milkhaus LDI-200; letrozol; leuprolide; leuprorelin; liarozole; lisuride hydrogen maleate; loxiglumide; mepitiothane; Leuprorelin; Ligand Pharmaceuticals LG-1127; LG-1447; LG-2293; LG-2527; LG-

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2716; Bone Care International LR-103; Lilly LY-326315; Lilly LY-353381-HCl; Lilly LY-326391; Lilly LY-353381; Lilly LY-357489; mifeprostone phosphate; Orion Pharma MPV-2213ad; Tulane University MZ-4-71; nafarelin; 5 nilutamide; Snow Brand NKS01; octreotide; Azko Nobel ORG-31710; Azko Nobel ORG-31806; orimeten; orimetene; orimetine; ormeloxifene; osaterone; Smithkline Beecham SKB-105657; Tokyo University OSW-1; Peptech PTL-03001; Pharmacia & Upjohn PNU-156765; quinagolide; ramorelix; Raloxifene; 10 statin; sandostatin LAR; Shionogi S-10364; Novartis SMT-487; somavert; somatostatin; tamoxifen; tamoxifen methiodide; teverelix; toremifene; triptorelin; TT-232; vapreotide; vorozole; Yamanouchi YM-116; Yamanouchi YM-511; Yamanouchi YM-55208; Yamanouchi YM-53789; Schering 15 AG ZK-1911703; Schering AG ZK-230211; and Zeneca ZD-182780.

Preferred hormonal agents that may be used in the present invention include, but are not limited to, those identified in Table No. 10, below.

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Table No. 10. Hormonal agents

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|----------------------------|----------|-----------|--------|
| 2-methoxyestradiol | EntreMed; 2-ME | EntreMed | | |
| N-(S)-tetrahydrofuroyl-Gly-D2Nal-D4ClPhe-D3Pal-Ser-NMeTyr-DLys(Nic)-Leu-Lys(Isp)-Pro-DAla-NH ₂ | A-84861 | Abbott | | |
| | raloxi- | | | |

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|----------------------------|--------------|-------------|--|
| | fene | | | |
| [3R-1-(2,2-Dimethoxyethyl)-3-((4-methylphenyl)aminocarbonylmethyl)-3-(N'-(4-methylphenyl)ureido)-indoline-2-one] | AG-041R | Chugai | WO 94/19322 | |
| | AN-207 | Asta Medica | WO 97/19954 | |
| Ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- | toremifene; FARESTON® | Orion Pharma | EP 95875 | 60 mg/d |
| Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- | tamoxifen NOLVADEX(R) | Zeneca | US 4536516 | For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be divided (morning and evening). |
| D-Alaninamide N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3- | Antide; ORF-23541 | Ares-Serono | WO 89/01944 | 25 or 50microg/kg sc |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|---------------------------------------|-------------------|------------|-----------|
| pyridinyl)-D-alanyl-L-seryl-N6-(3-pyridinylcarbonyl)-L-lysyl-N6-(3-pyridinylcarbonyl)-D-lysyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl- | | | | |
| | B2036-PEG; Somaver; Trovert | Sensus | | |
| 4-Methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-7-(pivaloyloxy)-3-[4-(pivaloyloxy)phenyl]-2H-1-benzopyran | EM-800; EM-652 | Laval University | | |
| | letrozol | | US 4749346 | |
| | goserelin | | US 4100274 | |
| 3-[4-[1,2-Diphenyl-1(Z)-butenyl]phenyl]-2(E)-propenoic acid | GW-5638 | Glaxo Wellcome | | |
| Estra-1,3,5(10)-triene-3,17-diol, 7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]-nonyl]-, (7alpha,17beta)- | ICI-182780; Faslodex; ZD-182780 | Zeneca | EP 34/6014 | 250mg/mth |
| | J015X | Tulane University | | |
| | LG-1127; LG-1447 | Ligand Pharmac | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|--|-------------------------|------------|------------|
| | | euticals | | |
| | LG-2293 | Ligand Pharmaceuticals | | |
| | LG-2527; LG-2716 | Ligand Pharmaceuticals | | |
| | buserelin, Peptech; deslorelin, Peptech; PTL-03001; triptorelin, Peptech | Peptech | | |
| | LR-103 | Bone Care International | | |
| [2-(4-Hydroxyphenyl)-6-hydroxynaphthalen-1-yl] [4-[2-(1-piperidinyl)ethoxy]phenyl]methane hydrochloride | LY-326315 | Lilly | WO 9609039 | |
| | LY-353381-HCl | Lilly | | |
| | LY-326391 | Lilly | | |
| | LY-353381 | Lilly | | |
| | LY-357489 | Lilly | | |
| | MPV-2213ad | Orion Pharma | EP 476944 | 0.3-300 mg |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|-----------------------------|--------------------|-----------|--------|
| Isobutyryl-Tyr-D-Arg-Asp-Ala-Ile-(4-Cl)-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-(2-aminobutyryl)-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-Ser 4-guanidinobutylamide | MZ-4-71 | Tulane University | | |
| Androst-4-ene-3,6,17-trione, 14-hydroxy- | NKS01; 14alpha-OHAT; 14OHAT | Snow Brand | EP 300062 | |
| 3beta,16beta,17alpha-trihydroxycholest-5-en-22-one-16-O-(2-O-4-methoxybenzoyl-beta-D-xylopyranosyl)-(1-3) (2-O-acetyl-alpha-L-arabinopyranoside) | OSW-1 | | | |
| Spiro[estra-4,9-diene-17,2' (3'H)-furan]-3-one, 11-[4-(dimethylamino)phenyl]-4',5'-dihydro-6-methyl-, (6beta,11beta,17beta)- | Org-31710; Org-31806 | Akzo Nobel | EP 289073 | |
| (22RS)-N-(1,1,1-trifluoro-2-phenylprop-2- | PNU-156765; FCE-28260 | Pharmacia & Upjohn | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|----------------------------|---------------------|-------------|--------|
| yl)-3-oxo-4-aza-5alpha-androst-1-ene-17beta -carboxamide | | | | |
| 1-[(benzofuran-2yl)-4-chlorophenylmethyl]imidazole | | Menarini | | |
| Tryptamine derivatives | | Rhone-Poulenc Rorer | WO 96/35686 | |
| Permanently ionic derivatives of steroid hormones and their antagonists | | Pharmos | WO 95/26720 | |
| Novel tetrahydronaphthofuranone derivatives | | Meiji Seika | WO 97/30040 | |
| | SMT-487; 90Y-octreotide | Novartis | | |
| D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH ₂ | TT-232 | | | |
| 2-(1H-imidazol-4-ylmethyl)-9H-carbazole monohydrochloride monohydrate | YM-116 | Yamanouchi | | |
| 4-[N-(4-bromobenzyl)-N-(4-cyanophenyl)amino]-4H-1,2,4-triazole | YM-511 | Yamanouchi | | |
| 2-(1H-imidazol- | YM-55208; | Yamanou | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---|-------------------------|------------|---------|
| 4-ylmethyl)-9H-carbazole monohydrochloride monohydrate | YM-53789 | -chi | | |
| | ZK-1911703 | Schering AG | | |
| | ZK-230211 | Schering AG | | |
| | abarelix | Praecis Pharmaceuticals | | |
| Androsta-5,16-dien-3-ol, 17-(3-pyridinyl)-, acetate (ester), (3beta)- | abiraterone acetate; CB-7598; CB-7630 | BTG | | |
| 2,6-Piperidinedione, 3-(4-aminophenyl)-3-ethyl- | aminoglutethimide; Ciba-16038; Cytadren; Elimina; Orimetene; Orimetene; Orimetine | Novartis | US 3944671 | |
| 1,3-Benzenediacetonitrile, alpha, alpha, alpha', alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)- | anastrozole; Arimidex; ICI-D1033; ZD-1033 | Zeneca | EP 296749 | 1mg/day |
| 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-2-methyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl- | avorelin; Meterelin | Mediolanum | EP 23904 | |

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|--|------------------------------|----------------|-----------------------|
| L-prolinamide | | | | |
| Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (+/-)- | bicalutam ide; Casodex; Cosudex; ICI- 176334 | Zeneca | EP 100172 | |
| Luteinizing hormone-releasing factor (pig), 6-[O-(1,1-dimethylethyl)-D-serine]-9-(N-ethyl-L-prolinamide)-10-deglycinamide- | busere- lin; Hoe- 766; Profact; Receptal; S-746766; Suprecor; Suprecur; Supre- fact; Suprefakt | Hoechst Marion Roussel | GB 15/23623 | 200-600 microg/day |
| D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N5-(aminocarbonyl)-D-ol-L-leucyl-L-arginyl-L-prolyl- | cetro- relix; SB-075; SB-75 | Asta Medica | EP 29/9402 | |
| Phosphonic acid, (dichloromethylene)bis-, disodium salt- | clodro- nate disodium, Leiras; Bonefos; Clasto- ban; KCO- 692 | Scherin g AG | | |
| Luteinizing hormone- | deslore- lin; | Roberts | US 4034082 | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|--|---------------------|------------|---------------|
| releasing factor (pig), 6-D-tryptophan-9-(N-ethyl-L-prolinamide)-10-deglycinamide- | gonado-relin analogue, Roberts; LHRH analogue, Roberts; Somagard | | | |
| Phenol, 3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]-, (E)-[CA S] | droloxi-fene; FK-435; K-060; K-21060E; RP 60850 | Klinge | EP 54168 | |
| 4-Azaandrost-1-ene-17-carboxamide, N-(2,5-bis(trifluoromethyl)phenyl)-3-oxo-, (5alpha,17beta)- | dutasteride; GG-745; GI-198745 | Glaxo Wellcome | | |
| Androstan-17-ol, 2,3-epithio-, (2alpha,3alpha,5alpha,17beta)- | epitio-stanol; 10275-S; epithioandrostan-ol; S-10275; Thiobres-tin; Thiodrol | Shionogi | US 3230215 | |
| Androsta-3,5-diene-3-carboxylic acid, 17-(((1,1-dimethylethyl)amino)carbonyl)-(17beta)- | epristeride; ONO-9302; SK&F-105657; SKB-105657 | Smith-Kline Beecham | EP 289327 | 0.4-160mg/day |
| estrone 3-O-sulfamate | estrone 3-O-sulfamate | | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|---|--------------------|------------|-------------|
| 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, 3-(2-propanesulfonate), (17 α)- | ethinyl estradiol sulfonate; J96; Turisteron | Schering AG | DE 1949095 | |
| Androsta-1,4-diene-3,17-dione, 6-methylene- | exemestane; FCE-24304 | Pharmacia & Upjohn | DE 3622841 | 5mg/kg |
| Benzonitrile, 4-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)-, monohydrochloride | fadrozole; Afema; Arensin; CGS-16949; CGS-16949A; CGS-20287; fadrozole monohydrochloride | Novartis | EP 165904 | 1 mg po bid |
| 4-Azaandrost-1-ene-17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-, (5 α ,17 β)- | finasteride; Andozac; ChibroProscar; Finastid; MK-0906; MK-906; Procure; Prodel; Propecia; Proscar; Proskar; Prostide; YM-152 | Merck & Co | EP 155096 | 5mg/day |
| Propanamide, 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]- | flutamide; Drogenil; Euflex; Eulexin; | Schering Plough | US 4329364 | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---|--------------|------------|---------------------------|
| | Eulexine; Flucinom; Flutamida ; Fugerel; NK-601; Odyne; Prostogen at; Sch- 13521 | | | |
| Androst-4-ene- 3,17-dione, 4- hydroxy- | formest- ane; 4- HAD; 4- OHA; CGP- 32349; CRC- 82/01; Depot; Lentaron | Novarti s | EP 346953 | 250 or 600mg/day po |
| [N-Ac-D-Nal, D- pCl-Phe, D-Pal, D- hArg(Et)2, hArg(E t)2, D-Ala]GnRH- | ganirel- ix; Org- 37462; RS-26306 | Roche | EP 312052 | |
| | gonadore- lin agonist, Shire | Shire | | |
| Luteinizing hormone- releasing factor (pig), 6-[O- (1,1- dimethylethyl)- D-serine] -10- deglycinamide-, 2- (aminocarbonyl)h ydrazide | goserel- in; ICI- 118630; Zoladex; Zoladex LA | Zeneca | US 4100274 | |
| | hCG; gonadotro phin; LDI-200 | Milkhau s | | |
| | human | NIH | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|--|-------------------|-----------|-----------|
| | chorionic gonadotrophin; hCG | | | |
| Pyrrolidine, 1-[2-[4-[1-(4-iodophenyl)-2-phenyl-1-butenyl]phenoxy]ethyl]-, (E)- | idoxifene; CB-7386; CB-7432; SB-223030 | BTG | EP 260066 | |
| | isocordoin | Indena | | |
| 2,4(1H,3H)-Quinazolin-3-one, 3-[2-[4-(4-fluorobenzoyl)-1-piperidinylethyl]- | ketanserin; Aseranox; Ketensin; KJK-945; ketanserin; Perketan; R-41468; Serefrex; Serepress; Sufrexal; Taseron | Johnson & Johnson | EP 13612 | |
| L-Threoninamide, 3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-, cyclic (2-7)-disulfide | lanreotide; Angiopeptin; BIM-23014; Dermopeptin; Ipstyl; Somatuline; Somatuline LP | Beaufour-Ipsen | EP 215171 | |
| Benzonitrile, 4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis- | letrozole; CGS-20267; Femara | Novartis | EP 236940 | 2.5mg/day |
| Luteinizing hormone- | leuprolide, | Atrix | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|--|---------|------------|-------------------------|
| releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamid e)-10-deglycinamide- | Atrigel; leuprolide, Atrix | | | |
| Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide- | leupror-elin; Abbott-43818; Carcinil; Enantone; Leuplin; Lucrin; Lupron; Lupron Depot; leuprolide, Abbott; leuprolide, Takeda; leupror-elin, Takeda; Procren Depot; Procrin; Prostap; Prostap SR; TAP-144-SR | Abbott | US 4005063 | 3.75microg sc q 28 days |
| Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-(N-ethyl-L-prolinamid e)-10-deglycinamide- | leupror-elin, DUROS; leuprolid e, DUROS; leupror-elin | Alza | | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|--|-------------------|-------------|-----------|
| 1H-Benzimidazole, 5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]- | liarozole; Liazal; Liazol; liarozole fumarate; R-75251; R-85246; Ro-85264 | Johnson & Johnson | EP 260744 | 300mg bid |
| Urea, N'-[(8 α)-9,10-didehydro-6-methylergolin-8-yl]-N,N-diethyl-, (Z)-2-butenedioate (1:1) | lisuride hydrogen maleate; Cuvalit; Dopergin; Dopergine; Eunal; Lysenyl; Lysenyl Forte; Revanil | VUFB | | |
| Pentanoic acid, 4-[(3,4-dichlorobenzoyl)amino]-5-[(3-methoxypropyl)pentylamino]-5-oxo-, (+/-)- | loxiglumide; CR-1505 | Rotta Research | WO 87/03869 | |
| Androstane, 2,3-epithio-17-[(1-methoxycyclopentyl)oxy]-, (2 α ,3 α ,5 α ,17 β) - | mepitiostane; S-10364; Thioderon | Shionogi | US 3567713 | |
| Phenol, 4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-[4-(1-methylethyl)phenyl]-1-butenyl]-, dihydrogen | miproxifene phosphate; DP-TAT-59; TAT-59 | Taiho | WO 87/07609 | 20mg/day |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---|------------------------|-------------|--------|
| phosphate (ester), (E)- | | | | |
| Luteinizing hormone-releasing factor (pig), 6-[3-(2-naphthalenyl)-D-alanine]- | nafarelin ; NAG, Syntex; Nasanyl; RS-94991; RS-94991-298; Synarel; Synarela; Synrelina | Roche | EP 21/234 | |
| 2,4-Imidazolidinedione, 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]- | nilutamide; Anandron; Nilandron; Notostaran; RU-23908 | Hoechst Marion Roussel | US 4472382 | |
| | obesity gene; diabetes gene; leptin | Lilly | WO 96/24670 | |
| L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2-7)-disulfide, [R-(R*,R*)]- | octreotide; Longastatina; octreotide pamoate; Sandostatine; Sandostatine LAR; Sandostatine; SMS-201-995 | Novartis | EP 29/579 | |
| Pyrrolidine, 1- | ormelox- | Central | DE 2329201 | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---|------------------------|-----------|--------|
| [2-(p-(7-methoxy-2,2-dimethyl-3-phenyl-4-chromanyl)phenoxy)ethyl]-, trans- | ifene; 6720-CDRI; Centron; Choice-7; centchroman; Saheli | Drug Research Inst. | | |
| 2-Oxapregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-chloro- | osaterone acetate; Hipros; TZP-4238 | Teikoku Hormone | EP 193871 | |
| Pregn-4-ene-3,20-dione | progesterone; Crinone | Columbia Laboratories | | |
| Sulfamide, N,N-diethyl-N'-(1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[g]quinolin-3-yl)-, (3alpha,4aalpha,10abeta)- (+/-)- | quinagolide; CV-205-502; Norprolac; SDZ-205-502 | Novartis | EP 77754 | |
| L-Proline, 1-(N2-(N-(N-(N-(N-(N-(N-(N-acetyl-3-(2-naphthalenyl)-D-alanyl)-4-chloro-D-phenylalanyl)-D-tryptophyl)-L-seryl)-L-tyrosyl)-O-(6-deoxy-alpha-L-mannopyranosyl)-D-seryl)-L-leucyl)-L-arginyl)-, 2-(aminocarbonyl)h | ramorelix; Hoe-013; Hoe-013C; Hoe-2013 | Hoechst Marion Roussel | EP 451791 | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|---|-------------------|------------|---------|
| ydrazide- | | | | |
| | somatostatin analogues | Tulane University | | |
| Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- | tamoxifen; Ceadan; ICI-46474; Kessar; Nolgen; Nolvadex; Tafoxen; Tamofen; Tamoplex; Tamoxas-ta; Tamoxen; Tomaxen | Zeneca | US 4536516 | |
| | tamoxifen methiodide | Pharmos | | |
| Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (z)- | tamoxifen | Douglas | | |
| D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-L-tyrosyl-N ⁶ -(aminocarbonyl)-D-lysyl-L-leucyl-N ⁶ -(1-methylethyl)-L-lysyl-L-prolyl- | teverelix; Antarelix | Asta Medica | | |
| Ethanamine, 2- | toremif- | Orion | EP 95875 | 60mg po |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---|-------------------------|------------|---------------------|
| [4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)- | ene; Estrimex; Fareston; FC-1157; FC-1157a; NK-622 | Pharma | | |
| Luteinizing hormone-releasing factor (pig), 6-D-tryptophan- | tripto- relin; ARVEKAP; AY-25650; BIM- 21003; BN-52104; Decap- eptyl; WY-42422 | Debio- pharm | US 4010125 | |
| L-Tryptophanamide, D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-, cyclic (2-7)-disulfide- | vapreot- ide; BMY- 41606; Octasta- tin; RC- 160 | Debio- pharm | EP 203031 | 500microg sc tid |
| 1H-Benzotriazole, 6-[(4-chlorophenyl)-1H-1,2,4-triazol-1-ylmethyl]-1-methyl- | vorozole; R-76713; R-83842; Rivizor | Johnson & Johnson | EP 293978 | 2.5mg/day |

A sixth family of antineoplastic agents which may be used in combination with the present invention consists of a miscellaneous family of antineoplastic agents including, but not limited to alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, 5 Kyorin AHC-52, alstonine, amonafide, amphetinile,

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amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, 5 benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, calcium carbonate, Calcet, Calci-Chew, Calci-Mix, Roxane calcium carbonate tablets, caracemide, carmethizole hydrochloride, 10 Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Cell Pathways CP-461, Yakult 15 Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, DFMO, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, 20 Daiichi Seiyaku DN-9693, docetaxel, Encore Pharmaceuticals E7869, elliprabin, elliptinium acetate, Tsumura EPMTTC, ergotamine, etoposide, etretinate, Eulexin®, Cell Pathways Exisulind® (sulindac sulphone or CP-246), fenretinide, Merck Research Labs Finasteride, 25 Florical, Fujisawa FR-57704, gallium nitrate, gemcitabine, genkwadaphnin, Gerimed, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, 30 ilmofofosine, irinotecan, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, ketoconazole, Otsuak K-

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76COONa, Kureha Chemical K-AM, MECT Corp KI-8110,
American Cyanamid L-623, leucovorin, levamisole,
leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-
186641, Materna, NCI (US) MAP, marycin, Merrel Dow MDL-
5 27048, Medco MEDR-340, megestrol, merbarone, merocyanine
derivatives, methylanilinoacridine, Molecular Genetics
MGI-136, minactivin, mitonafide, mitoquidone, Monocal,
mopidamol, motretinide, Zenyaku Kogyo MST-16, Mylanta,
N-(retinoyl)amino acids, Nilandron; Nisshin Flour
10 Milling N-021, N-acylated-dehydroalanines, nafazatrom,
Taisho NCU-190, Nephro-Calci tablets, nocodazole
derivative, Normosang, NCI NSC-145813, NCI NSC-361456,
NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112,
oquizanocine, Akzo Org-10172, paclitaxel,
15 pancratistatin, pazelliptine, Warner-Lambert PD-111707,
Warner-Lambert PD-115934, Warner-Lambert PD-131141,
Pierre Fabre PE-1001, ICRT peptide D, piroxantrone,
polyhaematoporphyrin, polypreic acid, Efamol porphyrin,
prohimane, procarbazine, proglumide, Invitron protease
20 nexin I, Tobishi RA-700, razoxane, retinoids, Encore
Pharmaceuticals R-flurbiprofen, Sandostatin; Sapporo
Breweries RBS, restrictin-P, retelliptine, retinoic
acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976,
Scherring-Plough SC-57050, Scherring-Plough SC-57068,
25 selenium(selenite and selenomethionine), SmithKline
SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm
SP-10094, spatol, spirocyclopropane derivatives,
spirogermanium, Unimed, SS Pharmaceutical SS-554,
strypoldinone, Stypoldione, Suntory SUN 0237, Suntory
30 SUN 2071, Sugan SU-101, Sugan SU-5416, Sugan SU-6668,
sulindac, sulindac sulfone; superoxide dismutase, Toyama

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T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine
 5 sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, Zileuton, ursodeoxycholic acid, and Zanosar.

Preferred miscellaneous agents that may be used in
 10 the present invention include, but are not limited to, those identified in Table No. 11, below.

Table No. 11. Miscellaneous agents

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|----------------------------|------------------------|-------------|---|
| Flutamide; 2-methyl- N-(4-nitro-3-(trifluoromethyl)phenyl) propanamide | EULEXIN® | Schering Corp | | 750 mg/d in 3 8-hr doses. |
| | Ketoconazole | | US 4144346 | |
| | leucovorin | | US 4148999 | |
| | irinotecan | | US 4604463 | |
| | levamisole | | GB 11/20406 | |
| | megestrol | | US 4696949 | |
| | paclitaxel | | US 5641803 | |
| Nilutamide 5,5-dimethyl 3-(4-nitro 3-(trifluoromethyl) phenyl) 2,4-imidazolidined | Nilandron | Hoechst Marion Roussel | | A total daily dose of 300 mg for 30 days followed thereafter by three |

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|---|----------------------------|------------------------|------------|--|
| ione | | | | tablets (50 mg each) once a day for a total daily dosage of 150 mg. |
| | Vinorelbine | | EP 0010458 | |
| | vinblastine | | | |
| | vincristine | | | |
| Octreotide acetate L-cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-NSAIDs- (2-hydroxy-1-(hydroxymethyl)propyl)-, cyclic-disulfide; (R-(R*,R*)) acetate salt | Sandostatin | Sandoz Pharmaceuticals | | s.c. or i.v. administration Acromegaly: 50 - 300 mcgm tid. Carcinoid tumors: 100 - 600 mcgm/d (mean = 300 mcgm/d) Vipomas: 200-300 mcgm in first two weeks of therapy |
| Streptozocin Streptozocin 2-deoxy-2-(((methylnitrosamino)carbonyl)amino)-alpha (and beta)-D-glucopyranose) | Zanosar | Pharmacia & Upjohn | | i.v. 1000 mg/M2 of body surface per week for two weeks. |
| | topotecan | | US 5004758 | |
| Selenium | | | EP 804927 | |

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| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|----------------------|----------------------------|---------------------------|------------|--------|
| L-selenomethionine | ACES® | J.R. Carlson Laboratories | | |
| calcium carbonate | | | | |
| sulindac sulfone | Exisuland® | | US 5858694 | |
| ursodeoxycholic acid | | | US 5843929 | |
| | Cell Pathways CP-461 | | | |

Some additional preferred antineoplastic agents include those described in the individual patents listed in Table No. 12 below, and are hereby individually incorporated by reference.

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Table No. 12. Antineoplastic agents

| | | | |
|--------------|-------------|-------------|--------------|
| EP 0296749 | EP 0882734 | EP 00253738 | GB 02/135425 |
| WO 09/832762 | EP 0236940 | US 5338732 | US 4418068 |
| US 4692434 | US 5464826 | US 5061793 | EP 0702961 |
| EP 0702961 | EP 0702962 | EP 0095875 | EP 0010458 |
| EP 0321122 | US 5041424 | JP 60019790 | WO 09/512606 |
| US 4,808614 | US 4526988 | CA 2128644 | US 5455270 |
| WO 99/25344 | WO 96/27014 | US 5695966 | DE 19547958 |
| WO 95/16693 | WO 82/03395 | US 5789000 | US 5902610 |
| EP 189990 | US 4500711 | FR 24/74032 | US 5925699 |
| WO 99/25344 | US 4537883 | US 4808614 | US 5464826 |
| US 5366734 | US 4767628 | US 4100274 | US 4584305 |
| US 4336381 | JP 5050383 | JP 5050384 | JP 5064281 |
| JP 51146482 | JP 5384981 | US 5472949 | US 5455270 |
| US 4140704 | US 4537883 | US 4814470 | US 3590028 |

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| | | | |
|-------------|-------------|-------------|-------------|
| US 4564675 | US 4526988 | US 4100274 | US 4604463 |
| US 4144346 | US 4749713 | US 4148999 | GB 11/20406 |
| US 4696949 | US 4310666 | US 5641803 | US 4418068 |
| US 5,004758 | EP 0095875 | EP 0010458 | US 4935437 |
| US 4,278689 | US 4820738 | US 4413141 | US 5843917 |
| US 5,858694 | US 4330559 | US 5851537 | US 4499072 |
| US 5,217886 | WO 98/25603 | WO 98/14188 | |

Table No. 13 provides illustrative examples of median dosages for selected cancer agents that may be used in combination with an antiangiogenic agent. It should be noted that specific dose regimen for the chemotherapeutic agents below depends upon dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular combination employed.

Table No. 13. Median dosages for selected cancer agents.

| | <u>NAME OF CHEMOTHERAPEUTIC AGENT</u> | <u>MEDIAN DOSAGE</u> |
|----|---|----------------------|
| 20 | Asparaginase | 10,000 units |
| | Bleomycin Sulfate | 15 units |
| | Carboplatin | 50-450 mg. |
| | Carmustine | 100 mg. |
| | Cisplatin | 10-50 mg. |

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| | | |
|----|--|-----------------|
| | Cladribine | 10 mg. |
| | Cyclophosphamide (lyophilized) | 100 mg.-2 gm. |
| 5 | Cyclophosphamide (non- lyophilized) | 100 mg.-2 gm. |
| | Cytarabine (lyophilized powder) | 100 mg.-2 gm. |
| | Dacarbazine | 100 mg.-200 mg. |
| | Dactinomycin | 0.5 mg. |
| 10 | Daunorubicin | 20 mg. |
| | Diethylstilbestrol | 250 mg. |
| | Doxorubicin | 10-150 mg. |
| | Etidronate | 300 mg. |
| | Etoposide | 100 mg. |
| 15 | Floxuridine | 500 mg. |
| | Fludarabine Phosphate | 50 mg. |
| | Fluorouracil | 500 mg.-5 gm. |
| | Goserelin | 3.6 mg. |
| | Granisetron Hydrochloride | 1 mg. |
| 20 | Idarubicin | 5-10 mg. |
| | Ifosfamide | 1-3 gm. |
| | Leucovorin Calcium | 50-350 mg. |
| | Leuprolide | 3.75-7.5 rng. |
| | Mechlorethamine | 10 mg. |
| 25 | Medroxyprogesterone | 1 gm. |
| | Melphalan | 50 gm. |
| | Methotrexate | 20 mg.-1 gm. |
| | Mitomycin | 5-40 mg. |
| | Mitoxantrone | 20-30 mg. |
| 30 | Ondansetron Hydrochloride | 40 mg. |
| | Paclitaxel | 30 mg. |

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| | | |
|----|----------------------|----------------------|
| | Pamidronate Disodium | 30-90 mg. |
| | Pegaspargase | 750 units |
| | Plicamycin | 2,500 mcgm. |
| | Streptozocin | 1 gm. |
| 5 | Thiotepa | 15 mg. |
| | Teniposide | 50 mg. |
| | Vinblastine | 10 mg. |
| | Vincristine | 1-5 mg. |
| | Aldesleukin | 22 million units |
| 10 | Epoetin Alfa | 2,000-10,000 units |
| | Filgrastim | 300-480 mcgm. |
| | Immune Globulin | 500 mg.-10 gm. |
| | Interferon Alpha-2a | 3-36 million units |
| | Interferon Alpha-2b | 3-50 million units |
| 15 | Levamisole | 50 mg. |
| | Octreotide | 1,000-5,000 mcgm. |
| | <u>Sargramostim</u> | <u>250-500 mcgm.</u> |

20 The anastrozole used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,935,437.

The capecitabine used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,472,949.

25 The carboplatin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,455,270.

The Cisplatin used in the therapeutic combinations of the present invention can be prepared in the manner
30 set forth in U.S. Patent No. 4,140,704.

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The cyclophosphamide used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,537,883.

5 The eflornithine (DFMO) used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,413,141.

The docetaxel used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,814,470.

10 The doxorubicin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 3,590,028.

The etoposide used in the therapeutic combinations of the present invention can be prepared in the manner
15 set forth in U.S. Patent No. 4,564,675.

The fluorouracil used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,336,381.

The gemcitabine used in the therapeutic
20 combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,526,988.

The goserelin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,100,274.

25 The irinotecan used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,604,463.

The ketoconazole used in the therapeutic combinations of the present invention can be prepared in
30 the manner set forth in U.S. Patent No. 4,144,346.

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The letrozole used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,749,713.

5 The leucovorin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,148,999.

The levamisole used in the therapeutic combinations of the present invention can be prepared in the manner set forth in GB 11/20,406.

10 The megestrol used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,696,949.

The mitoxantrone used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,310,666.

The paclitaxel used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,641,803.

20 The Retinoic acid used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,843,096.

The tamoxifen used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,418,068.

25 The topotecan used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,004,758.

The toremifene used in the therapeutic combinations of the present invention can be prepared in the manner set forth in EP 00/095,875.

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The vinorelbine used in the therapeutic combinations of the present invention can be prepared in the manner set forth in EP 00/010,458.

The sulindac sulfone used in the therapeutic
5 combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,858,694.

The selenium (selenomethionine) used in the therapeutic combinations of the present invention can be prepared in the manner set forth in EP 08/04,927.

10 The ursodeoxycholic acid used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/34,608. Ursodeoxycholic acid can also be prepared according to the manner set forth in EP 05/99,282. Finally, ursodeoxycholic acid can
15 be prepared according to the manner set forth in U.S. Patent No. 5,843,929.

Still more preferred antineoplastic agents include: anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461,
20 cyclophosphamide, docetaxel, doxorubicin, etoposide, Exisulind®, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid,
25 tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO).

The phrase "taxane" includes a family of diterpene
30 alkaloids all of which contain a particular eight (8) member "taxane" ring structure. Taxanes such as

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paclitaxel prevent the normal post division breakdown of microtubules which form to pull and separate the newly duplicated chromosome pairs to opposite poles of the cell prior to cell division. In cancer cells which are rapidly dividing, taxane therapy causes the microtubules to accumulate which ultimately prevents further division of the cancer cell. Taxane therapy also affects other cell processes dependant on microtubules such as cell motility, cell shape and intracellular transport. The major adverse side-effects associated with taxane therapy can be classified into cardiac effects, neurotoxicity, haematological toxicity, and hypersensitivity reactions. (See Exp. Opin. Thera. Patents (1998) 8(5), hereby incorporated by reference). Specific adverse side-effects include neutropenia, alopecia, bradycardia, cardiac conduction defects, acute hypersensitivity reactions, neuropathy, mucositis, dermatitis, extravascular fluid accumulation, arthralgias, and myalgias. Various treatment regimens have been developed in an effort to minimize the side effects of taxane therapy, but adverse side-effects remain the limiting factor in taxane therapy.

It has been recently discovered in vitro that COX-2 expression is elevated in cells treated with taxanes. Elevated levels of COX-2 expression are associated with inflammation and generation of other COX-2 derived prostaglandin side effects. Consequently, when taxane therapy is provided to a patient, the administration of a COX-2 inhibitor is contemplated to reduce the inflammatory and other COX-2 derived prostaglandin side effects associated with taxane therapy.

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Taxane derivatives have been found to be useful in treating refractory ovarian carcinoma, urothelial cancer, breast carcinoma, melanoma, non-small-cell lung carcinoma, gastric, and colon carcinomas, squamous carcinoma of the head and neck, lymphoblastic, myeloblastic leukemia, and carcinoma of the esophagus.

Paclitaxel is typically administered in a 15-420 mg/m² dose over a 6 to 24 hour infusion. For renal cell carcinoma, squamous carcinoma of head and neck, carcinoma of esophagus, small and non-small cell lung cancer, and breast cancer, paclitaxel is typically administered as a 250 mg/m² 24 hour infusion every 3 weeks. For refractory ovarian cancer paclitaxel is typically dose escalated starting at 110 mg/m².

Docetaxel is typically administered in a 60 - 100 mg/M² i.v. over 1 hour, every three weeks. It should be noted, however, that specific dose regimen depends upon dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular agents and combination employed.

In one embodiment, paclitaxel is used in the present invention in combination with a cyclooxygenase-2 inhibitor and a MMP inhibitor and with cisplatin, cyclophosphamide, or doxorubicin for the treatment of breast cancer. In another embodiment paclitaxel is used in combination with a cyclooxygenase-2 inhibitor and a

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MMP inhibitor, cisplatin or carboplatin, and ifosfamide for the treatment of ovarian cancer.

In another embodiment docetaxal is used in the present invention in combination with a cyclooxygenase-2 inhibitor and a MMP inhibitor and in combination with cisplatin, cyclophosphamide, or doxorubicin for the treatment of ovary and breast cancer and for patients with locally advanced or metastatic breast cancer who have progressed during anthracycline based therapy.

The following references listed in Table No. 14 below, hereby individually incorporated by reference herein, describe various taxanes and taxane derivatives suitable for use in the present invention, and processes for their manufacture.

Table No. 14. Taxanes and taxane derivatives

| | | | |
|------------|------------|------------|------------|
| EP 694539 | EP 683232 | EP 639577 | EP 627418 |
| EP 604910 | EP 797988 | EP 727492 | EP 767786 |
| EP 767376 | US 5886026 | US 5880131 | US 5879929 |
| US 5871979 | US 5869680 | US 5871979 | US 5854278 |
| US 5840930 | US 5840748 | US 5827831 | US 5824701 |
| US 5821363 | US 5821263 | US 5811292 | US 5808113 |
| US 5808102 | US 5807888 | US 5780653 | US 5773461 |
| US 5770745 | US 5767282 | US 5763628 | US 5760252 |
| US 5760251 | US 5756776 | US 5750737 | US 5744592 |
| US 5739362 | US 5728850 | US 5728725 | US 5723634 |
| US 5721268 | US 5717115 | US 5716981 | US 5714513 |
| US 5710287 | US 5705508 | US 5703247 | US 5703117 |
| US 5700669 | US 5693666 | US 5688977 | US 5684175 |
| US 5683715 | US 5679807 | US 5677462 | US 5675025 |
| US 5670673 | US 5654448 | US 5654447 | US 5646176 |
| US 5637732 | US 5637484 | US 5635531 | US 5631278 |

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| | | | |
|------------|-------------|-------------|-------------|
| US 5629433 | US 5622986 | US 5618952 | US 5616740 |
| US 5616739 | US 5614645 | US 5614549 | US 5608102 |
| US 5599820 | US 5594157 | US 5587489 | US 5580899 |
| US 5574156 | US 5567614 | US 5565478 | US 5560872 |
| US 5556878 | US 5547981 | US 5539103 | US 5532363 |
| US 5530020 | US 5508447 | US 5489601 | US 5484809 |
| US 5475011 | US 5473055 | US 5470866 | US 5466834 |
| US 5449790 | US 5442065 | US 5440056 | US 5430160 |
| US 5412116 | US 5412092 | US 5411984 | US 5407816 |
| US 5407674 | US 5405972 | US 5399726 | US 5395850 |
| US 5384399 | US 5380916 | US 5380751 | US 5367086 |
| US 5356928 | US 5356927 | US 5352806 | US 5350866 |
| US 5344775 | US 5338872 | US 5336785 | US 5319112 |
| US 5296506 | US 5294737 | US 5294637 | US 5284865 |
| US 5284864 | US 5283253 | US 5279949 | US 5274137 |
| US 5274124 | US 5272171 | US 5254703 | US 5254580 |
| US 5250683 | US 5243045 | US 5229526 | US 5227400 |
| US 5200534 | US 5194635 | US 5175,315 | US 5136060 |
| US 5015744 | WO 98/38862 | WO 95/24402 | WO 93/21173 |
| EP 681574 | EP 681575 | EP 568203 | EP 642503 |
| EP 667772 | EP 668762 | EP 679082 | EP 681573 |
| EP 688212 | EP 690712 | EP 690853 | EP 710223 |
| EP 534708 | EP 534709 | EP 605638 | EP 669918 |
| EP 855909 | EP 605638 | EP 428376 | EP 428376 |
| EP 534707 | EP 605637 | EP 679156 | EP 689436 |
| EP 690867 | EP 605637 | EP 690867 | EP 687260 |
| EP 690711 | EP 400971 | EP 690711 | EP 400971 |
| EP 690711 | EP 884314 | EP 568203 | EP 534706 |
| EP 428376 | EP 534707 | EP 400971 | EP 669918 |
| EP 605637 | US 5015744 | US 5175315 | US 5243045 |

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| | | | |
|-------------|-------------|-------------|-------------|
| US 5283253 | US 5250683 | US 5254703 | US 5274124 |
| US 5284864 | US 5284865 | US 5350866 | US 5227400 |
| US 5229526 | US 4876399 | US 5136060 | US 5336785 |
| US 5710287 | US 5714513 | US 5717115 | US 5721268 |
| US 5723634 | US 5728725 | US 5728850 | US 5739362 |
| US 5760219 | US 5760252 | US 5384399 | US 5399726 |
| US 5405972 | US 5430160 | US 5466834 | US 5489601 |
| US 5532363 | US 5539103 | US 5574156 | US 5587489 |
| US 5618952 | US 5637732 | US 5654447 | US 4942184 |
| US 5059699 | US 5157149 | US 5202488 | US 5750736 |
| US 5202488 | US 5549830 | US 5281727 | US 5019504 |
| US 4857653 | US 4924011 | US 5733388 | US 5696153 |
| WO 93/06093 | WO 93/06094 | WO 94/10996 | WO 9/10997 |
| WO 94/11362 | WO 94/15599 | WO 94/15929 | WO 94/17050 |
| WO 94/17051 | WO 94/17052 | WO 94/20088 | WO 94/20485 |
| WO 94/21250 | WO 94/21251 | WO 94/21252 | WO 94/21623 |
| WO 94/21651 | WO 95/03265 | WO 97/09979 | WO 97/42181 |
| WO 99/08986 | WO 99/09021 | WO 93/06079 | US 5202448 |
| US 5019504 | US 4857653 | US 4924011 | WO 97/15571 |
| WO 96/38138 | US 5489589 | EP 781778 | WO 96/11683 |
| EP 639577 | EP 747385 | US 5422364 | WO 95/11020 |
| EP 747372 | WO 96/36622 | US 5599820 | WO 97/10234 |
| WO 96/21658 | WO 97/23472 | US 5550261 | WO 95/20582 |
| WO 97/28156 | WO 96/14309 | WO 97/32587 | WO 96/28435 |
| WO 96/03394 | WO 95/25728 | WO 94/29288 | WO 96/00724 |
| WO 95/02400 | EP 694539 | WO 95/24402 | WO 93/10121 |
| WO 97/19086 | WO 97/20835 | WO 96/14745 | WO 96/36335 |

U.S. Patent No. 5,019,504 describes the isolation of paclitaxel and related alkaloids from culture grown *Taxus brevifolia* cells.

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U.S. Patent No. 5,675,025 describes methods for synthesis of Taxol®, Taxol® analogues and intermediates from baccatin III.

U.S. Patent No. 5,688,977 describes the synthesis
5 of Docetaxel from 10-deacetyl baccatin III.

U.S. Patent No. 5,202,488 describes the conversion of partially purified taxane mixture to baccatin III.

U.S. Patent No. 5,869,680 describes the process of preparing taxane derivatives.

10 U.S. Patent No. 5,856,532 describes the process of the production of Taxol®.

U.S. Patent No. 5,750,737 describes the method for paclitaxel synthesis.

U.S. Patent No. 6,688,977 describes methods for
15 docetaxel synthesis.

U.S. Patent No. 5,677,462 describes the process of preparing taxane derivatives.

U.S. Patent No. 5,594,157 describes the process of making Taxol® derivatives.

20 Some preferred taxanes and taxane derivatives are described in the patents listed in Table No. 15 below, and are hereby individually incorporated by reference herein.

Table No. 15. Some preferred taxanes and taxane
25 derivatives

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| | | | |
|------------|------------|------------|-------------|
| US 5015744 | US 5136060 | US 5175315 | US 5200534 |
| US 5194635 | US 5227400 | US 4924012 | US 5641803 |
| US 5059699 | US 5157049 | US 4942184 | US 4960790 |
| US 5202488 | US 5675025 | US 5688977 | US 5750736 |
| US 5684175 | US 5019504 | US 4814470 | WO 95/01969 |

The phrase "retinoid" includes compounds which are natural and synthetic analogues of retinol (Vitamin A). The retinoids bind to one or more retinoic acid receptors to initiate diverse processes such as reproduction, development, bone formation, cellular proliferation and differentiation, apoptosis, hematopoiesis, immune function and vision. Retinoids are required to maintain normal differentiation and proliferation of almost all cells and have been shown to reverse/suppress carcinogenesis in a variety of in vitro and in vivo experimental models of cancer, see (Moon et al., Ch. 14 Retinoids and cancer. *In The Retinoids*, Vol. 2. Academic Press, Inc. 1984). Also see Roberts et al. Cellular biology and biochemistry of the retinoids. *In The Retinoids*, Vol. 2. Academic Press, Inc. 1984, hereby incorporated by reference), which also shows that vesanoid (tretinoid trans retinoic acid) is indicated for induction of remission in patients with acute promyelocytic leukemia (APL).

A synthetic description of retinoid compounds, hereby incorporated by reference, is described in: Dawson MI and Hobbs PD. The synthetic chemistry of

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retinoids: in The retinoids, 2nd edition. MB Sporn, AB Roberts, and DS Goodman(eds). New York: Raven Press, 1994, pp 5-178.

Lingen et al. describe the use of retinoic acid and
5 interferon alpha against head and neck squamous cell carcinoma (Lingen, MW et al., Retinoic acid and interferon alpha act synergistically as antiangiogenic and antitumor agents against human head and neck squamous cell carcinoma. Cancer Research 58 (23) 5551-
10 5558 (1998), hereby incorporated by reference).

Iurlaro et al. describe the use of beta interferon and 13-cis retinoic acid to inhibit angiogenesis.
(Iurlaro, M et al., Beta interferon inhibits HIV-1 Tat-induced angiogenesis: synergism with 13-cis retinoic
15 acid. European Journal of Cancer 34 (4) 570-576 (1998), hereby incorporated by reference).

Majewski et al. describe Vitamin D3 and retinoids in the inhibition of tumor cell-induced angiogenesis.
(Majewski, S et al., Vitamin D3 is a potent inhibitor of
20 tumor cell-induced angiogenesis. J. Invest. Dermatology. Symposium Proceedings, 1 (1), 97-101 (1996), hereby incorporated by reference).

Majewski et al. describe the role of retinoids and other factors in tumor angiogenesis. Majewski, S et al.,
25 Role of cytokines, retinoids and other factors in tumor angiogenesis. Central-European journal of Immunology 21 (4) 281-289 (1996), hereby incorporated by reference).

Bollag describes retinoids and alpha-interferon in the prevention and treatment of neoplastic disease.
30 (Bollag W. Retinoids and alpha-interferon in the prevention and treatment of preneoplastic and neoplastic

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diseases. Chemotherapie Journal, (Suppl) 5 (10) 55-64 (1996), hereby incorporated by reference.

Bigg, HF et al. describe all-trans retinoic acid with basic fibroblast growth factor and epidermal growth factor to stimulate tissue inhibitor of metalloproteinases from fibroblasts. (Bigg, HF et al., All-trans-retinoic acid interacts synergistically with basic fibroblast growth factor and epidermal growth factor to stimulate the production of tissue inhibitor of metalloproteinases from fibroblasts. Arch. Biochem. Biophys. 319 (1) 74-83 (1995), hereby incorporated by reference).

Nonlimiting examples of retinoids that may be used in the present invention are identified in Table No. 16 below.

Table No. 16. Retinoids

| Compound | Common Name/ Trade Name | Company | Reference | Dosage |
|--|---------------------------------------|-------------------|---------------|--|
| CD-271 | Adapaline | | EP 199636 | |
| Tretinoin trans retinoic acid | Vesanoid | Roche Holdings | | 45 mg/M ² /day as two evenly divided doses until complete remission |
| 2,4,6,8- Nonatetraen oic acid, | etretinate isoetret- in; Ro-10- | Roche Holdings | US 4215215 | .25 - 1.5 mg/kg/day |

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| | | | | |
|--|---|----------------------|------------|-------------------|
| 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-4-ethyl ester, (all-E)- | 9359; Ro-13-7652; Tegison; Tigason | | | |
| Retinoic acid, 13-cis- | isotretinoin Accutane; Isotrex; Ro-4-3780; Roaccutan; Roaccutane | Roche Holdings | US 4843096 | .5 to 2 mg/kg/day |
| | Roche Ro-40-0655 | Roche Holdings | | |
| | Roche Ro-25-6760 | Roche Holdings | | |
| | Roche Ro-25-9022 | Roche Holdings | | |
| | Roche Ro-25-9716 | Roche Holdings | | |
| Benzoic acid, 4-[[3,5-bis(trimethylsilyl)benzoyl]amino] | TAC-101 | Taiho Pharmaceutical | | |

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| | | | | |
|--|---|---|----------------|---|
| - | | | | |
| Retinamide, N-(4- hydroxyphen yl)- | fenretinid e 4-HPR; HPR; McN- R-1967 | | | 50 - 400 mg/kg/day |
| (2E,4E,6E) - 7-(3,5-Di- tert- butylphenyl) -3- methylocta- 2,4,6- trienoic acid | LGD-1550 ALRT-1550; ALRT-550; LG-1550 | Ligand Pharma- ceuticas ; Allergan USA | | 20 microg/m2 /day to 400 microg/m2 /day administe red as a single daily oral dose |
| | Molecular Design MDI-101 | | US 4885311 | |
| | Molecular Design MDI-403 | | US 4677120 | |
| Benzoic acid, 4-(1- (5,6,7,8- tetrahydro- 3,5,5,8,8- pentamethyl -2- naphthaleny l)eth | bexarotene LG-1064; LG-1069; LGD-1069; Targretin; Targretin Oral; Targretin Topical | | WO 94/15901 | |

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| | | | | |
|--|--|---------------------------------|----------------|--|
| enyl)- | Gel | | | |
| Benzoic acid, 4-(1- (5,6,7,8- tetrahydro- 3,5,8,8- pentamethyl -2- naphthaleny l)ethen yl)- | bexarotene , soft gel bexarotene , Ligand; bexaroten | R P Scherer | | |
| (2E,4E)-3- methyl-5- [3- (5,5,8,8- tetramethyl -5,6,7,8- tetrahydro- naphthalen- 2-yl)- thiopen-2- yl]-penta- 2,4-dienoic acid | | | WO 96/05165 | |
| | SR-11262 F | Hoffmann -La Roche Ltd | | |
| | BMS-181162 | Bristol Myers Squibb | EP 476682 | |

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| | | | | |
|-------------------------------|------------------------|--------------|--------------------------------------|--|
| N-(4-hydroxyphenyl)retinamide | IIT Research Institute | | Cancer Research 39, 1339-1346 (1979) | |
| | AGN-193174 | Allergan USA | WO 96/33716 | |

The following individual patent references listed in Table No. 17 below, hereby individually incorporated by reference, describe various retinoid and retinoid derivatives suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 17. Retinoids

| | | | |
|-------------|-------------|-------------|-------------|
| US 4215215 | US 4885311 | US 4677120 | US 4105681 |
| US 5260059 | US 4503035 | US 5827836 | US 3878202 |
| US 4843096 | WO 96/05165 | WO 97/34869 | WO 97/49704 |
| EP 19/9636 | WO 96/33716 | WO 97/24116 | WO 97/09297 |
| WO 98/36742 | WO 97/25969 | WO 96/11686 | WO 94/15901 |
| WO 97/24116 | CH 61/6134 | DE 2854354 | EP 579915 |
| US 5547947 | EP 552624 | EP 728742 | EP 331983 |
| EP 476682 | | | |

Some preferred retinoids include Accutane;
 10 Adapalene; Allergan AGN-193174; Allergan AGN-193676;

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Allergan AGN-193836; Allergan AGN-193109; Aronex AR-623; BMS-181162; Galderma CD-437; Eisai ER-34617; Etrinate; Fenretinide; Ligand LGD-1550; lexacalcitol; Maxia Pharmaceuticals MX-781; mofarotene; Molecular Design MDI-101; Molecular Design MDI-301; Molecular Design MDI-403; Motretinide; Eisai 4-(2-[5-(4-methyl-7-ethylbenzofuran-2-yl)pyrrolyl]) benzoic acid; Johnson & Johnson N-[4-[2-thyl-1-(1H-imidazol-1-yl)butyl]phenyl]-2-benzothiazolamine; Soriatane; Roche SR- 11262; Tocoretinate; Advanced Polymer Systems trans-retinoic acid; UAB Research Foundation UAB-8; Tazorac; TopiCare; Taiho TAC-101; and Vesanoid.

cGMP phosphodiesterase inhibitors, including Sulindac sulfone (Exisuland®) and CP-461 for example, are apoptosis inducers and do not inhibit the cyclooxygenase pathways. cGMP phosphodiesterase inhibitors increase apoptosis in tumor cells without arresting the normal cycle of cell division or altering the cell's expression of the p53 gene.

Ornithine decarboxylase is a key enzyme in the polyamine synthesis pathway that is elevated in most tumors and premalignant lesions. Induction of cell growth and proliferation is associated with dramatic increases in ornithine decarboxylase activity and subsequent polyamine synthesis. Further, blocking the formation of polyamines slows or arrests growth in transformed cells. Consequently, polyamines are thought to play a role in tumor growth. Difluoromethylornithine (DFMO) is a potent inhibitor of ornithine decarboxylase that has been shown to inhibit carcinogen-induced cancer development in a variety of rodent models (Meyskens et

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al. Development of Difluoromethylornithine (DFMO) as a chemoprevention agent. Clin. Cancer Res. 1999 May, 5(%):945-951, hereby incorporated by reference, herein). DFMO is also known as 2-difluoromethyl-2,5-
5 diaminopentanoic acid, or 2-difluoromethyl-2,5-diaminovaleric acid, or a-(difluoromethyl) ornithine; DFMO is marketed under the tradename Elformithine®. Therefore, the use of DFMO in combination with COX-2 inhibitors is contemplated to treat or prevent cancer,
10 including but not limited to colon cancer or colonic polyps.

Populations with high levels of dietary calcium have been reported to be protected from colon cancer. In vivo, calcium carbonate has been shown to inhibit colon
15 cancer via a mechanism of action independent from COX-2 inhibition. Further, calcium carbonate is well tolerated. A combination therapy consisting of calcium carbonate and a selective COX-2 inhibitor is contemplated to treat or prevent cancer, including but
20 not limited to colon cancer or colonic polyps.

Several studies have focused attention on bile acids as a potential mediator of the dietary influence on colorectal cancer risk. Bile acids are important detergents for fat solubilization and digestion in the
25 proximal intestine. Specific transprot processes in the apical domain of the terminal ileal enterocyte and basolateral domain of the hepatocyte account for the efficient conservation in the enterohepatic circulation. Only a small fraction of bile acids enter the colon;
30 however, perturbations of the cycling rate of bile acids by diet (e.g. fat) or surgery may increase the fecal

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bile load and perhaps account for the associated increased risk of colon cancer. (Hill MJ, Bile flow and colon cancer. 238 Mutation Review, 313 (1990).

Ursodeoxycholate (URSO), the hydrophilic 7-beta epimer
5 of chenodeoxycholate, is non cytotoxic in a variety of cell model systems including colonic epithelia. URSO is also virtually free of side effects. URSO, at doses of 15mg/kg/day used primarily in biliary cirrhosis trials were extremely well tolerated and without toxicity.

10 (Pourpon et al., A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. 324 New Engl. J. Med. 1548 (1991)). While the precise mechanism of URSO action is unknown, beneficial effects of URSO therapy are related to the enrichment of the
15 hepatic bile acid pool with this hydrophilic bile acid. It has thus been hypothesized that bile acids more hydrophilic than URSO will have even greater beneficial effects than URSO. For example, tauroursodeoxycholate (TURSO) the taurine conjugate of URSO. Non-steroidal
20 anti-inflammatory drugs (NSAIDs) can inhibit the neoplastic transformation of colorectal epithelium. The likely mechanism to explain this chemopreventive effect is inhibition of prostaglandin synthesis. NSAIDs inhibit cyclooxygenase, the enzyme that converts arachidonic
25 acid to prostaglandins and thromboxanes. However, the potential chemopreventive benefits of NSAIDs such as sulindac or mesalamine are tempered by their well known toxicities and moderately high risk of intolerance. Abdominal pain, dyspepsia, nausea, diarrhea,
30 constipation, rash, dizziness, or headaches have been reported in up to 9% of patients. The elderly appear to

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be particularly vulnerable as the incidence of NSAID-induced gastroduodenal ulcer disease, including gastrointestinal bleeding, is higher in those over the age of 60; this is also the age group most likely to develop colon cancer, and therefore most likely to benefit from chemoprevention. The gastrointestinal side effects associated with NSAID use result from the inhibition of cyclooxygenase-1, an enzyme responsible for maintenance of the gastric mucosa. Therefore, the use of COX-2 inhibitors in combination with URSO is contemplated to treat or prevent cancer, including but not limited to colon cancer or colonic polyps; it is contemplated that this treatment will result in lower gastrointestinal side effects than the combination of standard NSAIDs and URSO.

An additional class of antineoplastic agents that may be used in the present invention include nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). However, for the purposes of the present invention the definition of an NSAID does not include the "cyclooxygenase-2 inhibitors" described herein. Thus the phrase "nonsteroidal antiinflammatory drug" or "NSAID" includes agents that specifically inhibit cyclooxygenase-1, without significant inhibition of cyclooxygenase-2; or inhibit cyclooxygenase-1 and cyclooxygenase-2 at substantially the same potency; or inhibit neither cyclooxygenase-1 or cyclooxygenase-2. The potency and selectivity for the enzyme

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cyclooxygenase-1 and cyclooxygenase-2 can be determined by assays well known in the art, see for example, Cromlish and Kennedy, Biochemical Pharmacology, Vol. 52, pp 1777-1785, 1996.

- 5 Examples of NSAIDs that can be used in the combinations of the present invention include sulindac, indomethacin, naproxen, diclofenac, tolectin, fenoprofen, phenylbutazone, piroxicam, ibuprofen, ketophen, mefenamic acid, tolmetin, flufenamic acid,
- 10 nimesulide, niflumic acid, piroxicam, tenoxicam, phenylbutazone, fenclofenac, flurbiprofen, ketoprofen, fenoprofen, acetaminophen, salicylate and aspirin.

- The term "clinical tumor" includes neoplasms that are identifiable through clinical screening or
- 15 diagnostic procedures including, but not limited to, palpation, biopsy, cell proliferation index, endoscopy, mammagraphy, digital mammagraphy, ultrasonography, computed tomagraphy (CT), magnetic resonance imaging (MRI), positron emmission tomaagraphy (PET),
- 20 radiography, radionuclide evaluation, CT- or MRI-guided aspiration cytology, and imaging-guided needle biopsy, among others. Such diagnostic techniques are well known to those skilled in the art and are described in Cancer Medicine 4th Edition, Volume One. J.F. Holland, R.C.
- 25 Bast, D.L. Morton, E. Frei III, D.W. Kufe, and R.R. Weichselbaum (Editors). Williams & Wilkins, Baltimore (1997).

- The term "tumor marker" or "tumor biomarker" encompasses a wide variety of molecules with divergent
- 30 characteristics that appear in body fluids or tissue in association with a clinical tumor and also includes

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tumor-associated chromosomal changes. Tumor markers fall primarily into three categories: molecular or cellular markers, chromosomal markers, and serological or serum markers. Molecular and chromosomal markers complement
5 standard parameters used to describe a tumor (i.e. histopathology, grade, tumor size) and are used primarily in refining disease diagnosis and prognosis after clinical manifestation. Serum markers can often be measured many months before clinical tumor detection
10 and are thus useful as an early diagnostic test, in patient monitoring, and in therapy evaluation.

Molecular Tumor Markers

Molecular markers of cancer are products of cancer cells or molecular changes that take place in cells
15 because of activation of cell division or inhibition of apoptosis. Expression of these markers can predict a cell's malignant potential. Because cellular markers are not secreted, tumor tissue samples are generally required for their detection. Non-limiting examples of
20 molecular tumor markers that can be used in the present invention are listed in Table No. 1, below.

Table No. 1. Non-limiting Examples of Molecular Tumor Markers

| Tumor | Marker |
|--------------------|---------------------------------|
| Breast | p53 |
| Breast, Ovarian | ErbB-2/Her-2 |
| Breast | S phase and ploidy |
| Breast | pS2 |
| Breast | MDR2 |
| Breast | urokinase plasminogen activator |

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| | |
|------------------------|------------|
| Breast, Colon, Lung | myc family |
|------------------------|------------|

Chromosomal Tumor Markers

Somatic mutations and chromosomal aberrations have been associated with a variety of tumors. Since the identification of the Philadelphia Chromosome by Nowel and Hungerford, a wide effort to identify tumor-specific chromosomal alterations has ensued. Chromosomal cancer markers, like cellular markers, are can be used in the diagnosis and prognosis of cancer. In addition to the diagnostic and prognostic implications of chromosomal alterations, it is hypothesized that germ-line mutations can be used to predict the likelihood that a particular person will develop a given type of tumor. Non-limiting examples of chromosomal tumor markers that can be used in the present invention are listed in Table No. 2, below.

Table No. 2. Non-limiting Examples of Chromosomal Tumor Markers

| Tumor | Marker |
|--------|---------------------------------------|
| Breast | 1p36 loss |
| Breast | 6q24-27 loss |
| Breast | 11q22-23 loss |
| Breast | 11q13 amplification |
| Breast | TP53 mutation |
| Colon | Gain of chromosome 13 |
| Colon | Deletion of short arm of chromosome 1 |
| Lung | Loss of 3p |
| Lung | Loss of 13q |
| Lung | Loss of 17p |

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| | |
|------|------------|
| Lung | Loss of 9p |
|------|------------|

Serological Tumor Markers

Serum markers including soluble antigens, enzymes and hormones comprise a third category of tumor markers.

5 Monitoring serum tumor marker concentrations during therapy provides an early indication of tumor recurrence and of therapy efficacy. Serum markers are advantageous for patient surveillance compared to chromosomal and cellular markers because serum samples are more easily

10 obtainable than tissue samples, and because serum assays can be performed serially and more rapidly. Serum tumor markers can be used to determine appropriate therapeutic doses within individual patients. For example, the efficacy of a combination regimen consisting of

15 chemotherapeutic and antiangiogenic agents can be measured by monitoring the relevant serum cancer marker levels. Moreover, an efficacious therapy dose can be achieved by modulating the therapeutic dose so as to keep the particular serum tumor marker concentration

20 stable or within the reference range, which may vary depending upon the indication. The amount of therapy can then be modulated specifically for each patient so as to minimize side effects while still maintaining stable, reference range tumor marker levels. Table No.

25 3 provides non-limiting examples of serological tumor markers that can be used in the present invention.

Table No. 3. Non-limiting Examples of Serum Tumor Markers

| Cancer Type | Marker |
|-------------|--------|
|-------------|--------|

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| | |
|------------------|---|
| Germ Cell Tumors | a-fetoprotein (AFP) |
| Germ Cell Tumors | human chorionic gonadotrophin (hCG) |
| Germ Cell Tumors | placental alkaline phosphatase (PLAP) |
| Germ Cell Tumors | lactate dehydrogenase (LDH) |
| Prostate | prostate specific antigen (PSA) |
| Breast | carcinoembryonic antigen (CEA) |
| Breast | MUC-1 antigen (CA15-3) |
| Breast | tissue polypeptide antigen (TPA) |
| Breast | tissue polypeptide specific antigen (TPS) |
| Breast | CYFRA 21.1 |
| Breast | soluble <i>erb</i> -B-2 |
| Ovarian | CA125 |
| Ovarian | OVX1 |
| Ovarian | cancer antigen CA72-4 |
| Ovarian | TPA |
| Ovarian | TPS |
| Gastrointestinal | CD44v6 |
| Gastrointestinal | CEA |
| Gastrointestinal | cancer antigen CA19-9 |
| Gastrointestinal | NCC-ST-439 antigen (Dukes C) |
| Gastrointestinal | cancer antigen CA242 |
| Gastrointestinal | soluble <i>erb</i> -B-2 |
| Gastrointestinal | cancer antigen CA195 |

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| | |
|-------------------|--|
| Gastrointestinal | TPA |
| Gastrointestinal | YKL-40 |
| Gastrointestinal | TPS |
| Esophageal | CYFRA 21-1 |
| Esophageal | TPA |
| Esophageal | TPS |
| Esophageal | cancer antigen CA19-9 |
| Gastric Cancer | CEA |
| Gastric Cancer | cancer antigen CA19-9 |
| Gastric Cancer | cancer antigen CA72-4 |
| Lung | neruon specific enolase (NSE) |
| Lung | CEA |
| \Lung | CYFRA 21-1 |
| Lung | cancer antigen CA 125 |
| Lung | TPA |
| Lung | squamous cell carcinoma antigen (SCC) |
| Pancreatic cancer | ca19-9 |
| Pancreatic cancer | ca50 |
| Pancreatic cancer | ca119 |
| Pancreatic cancer | ca125 |
| Pancreatic cancer | CEA |
| Pancreatic cancer | |
| Renal Cancer | CD44v6 |
| Renal Cancer | E-cadherin |
| Renal Cancer | PCNA (proliferating cell nuclear antigen) |

Examples

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Germ Cell Cancers

Non-limiting examples of tumor markers useful in the present invention for the detection of germ cell cancers include, but are not limited to, a-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and its beta subunit (hCGb), lactate dehydrogenase (LDH), and placental alkaline phosphatase (PLAP).

AFP has an upper reference limit of approximately -10 kU/L after the first year of life and may be elevated in germ cell tumors, hepatocellular carcinoma and also in gastric, colon, biliary, pancreatic and lung cancers. AFP serum half life is approximately five days after orchidectomy. According to EGTM recommendations, AFP serum levels less than 1,000 kU/L correlate with a good prognosis, AFP levels between 1,000 and 10,000 kU/L, inclusive, correlate with intermediate prognosis, and AFP levels greater than 10,000 U/L correlate with a poor prognosis.

HCG is synthesized in the placenta and is also produced by malignant cells. Serum hCG concentrations may be increased in pancreatic adenocarcinomas, islet cell tumors, tumors of the small and large bowel, hepatoma, stomach, lung, ovaries, breast and kidney. Because some tumors only hCGb, measurement of both hCG and hCGb is recommended. Normally, serum hCG in men and pre-menopausal women is as high as -5 U/L while post-menopausal women have levels up to -10 U/L. Serum half life of hCG ranges from 16-24 hours. According to the EGTM, hCG serum levels under 5000 U/L correlate with a good prognosis, levels between 5000 and 50000 U/L, inclusively correlate with an intermediate prognosis,

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and hCG serum levels greater than 50000 U/L correlate with a poor prognosis. Further, normal hCG half lives correlate with good prognosis while prolonged half lives correlate with poor prognosis.

5 LDH is an enzyme expressed in cardiac and skeletal muscle as well as in other organs. The LDH-1 isoenzyme is most commonly found in testicular germ cell tumors but can also occur in a variety of benign conditions such as skeletal muscle disease and myocardial
10 infarction. Total LDH is used to measure independent prognostic value in patients with advanced germ cell tumors. LDH levels less than 1.5 x the reference range are associated with a good prognosis, levels between 1.5 and 10 x the reference range, inclusive, are associated
15 with an intermediate prognosis, and levels more than 10 x the reference range are associated with a poor prognosis.

PLAP is a enzyme of alkaline phosphatase normally expressed by placental syncytiotrophoblasts. Elevated
20 serum concentrations of PLAP are found in seminomas, non-seminomatous tumors, and ovarian tumors, and may also provide a marker for testicular tumors. PLAP has a normal half life after surgical resection of between 0.6 and 2.8 days.

25 Prostate Cancer

A nonlimiting example of a tumor marker useful in the present invention for the detection of prostate cancer is prostate specific antigen (PSA). PSA is a glycoprotein that is almost exclusively produced in the
30 prostate. In human serum, uncomplexed f-PSA and a complex of f-PSA with α_1 -antichymotrypsin make up total

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PSA (t-PSA). T-PSA is useful in determining prognosis in patients that are not currently undergoing anti-androgen treatment. Rising t-PSA levels via serial measurement indicate the presence of residual disease.

5 Breast Cancer

Non-limiting examples of serum tumor markers useful in the present invention for the detection of breast cancer include, but is not limited to carcinoembryonic antigen (CEA) and MUC-1 (CA 15.3). Serum CEA and CA15.3
10 levels are elevated in patients with node involvement compared to patients without node involvement, and in patients with larger tumors compared to smaller tumors. Normal range cutoff points (upper limit) are 5-10 mg/L for CEA and 35-60 u/ml for CA15.3. Additional
15 specificity (99.3%) is gained by confirming serum levels with two serial increases of more than 15%.

Ovarian Cancer

A non-limiting example of a tumor marker useful in the present invention for the detection of ovarian
20 cancer is CA125. Normally, women have serum CA125 levels between 0-35 kU/L; 99% of post-menopausal women have levels below 20 kU/L. Serum concentration of CA125 after chemotherapy is a strong predictor of outcome as elevated CA125 levels are found in roughly 80% of all
25 patients with epithelial ovarian cancer. Further, prolonged CA125 half-life or a less than 7-fold decrease during early treatment is also a predictor of poor disease prognosis.

Gastrointestinal Cancers

30 A non-limiting example of a tumor marker useful in the present invention for the detection of colon cancer

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is carcinoembryonic antigen (CEA). CEA is a glycoprotein produced during embryonal and fetal development and has a high sensitivity for advanced carcinomas including those of the colon, breast, stomach and lung. High pre-
5 or postoperative concentrations (>2.5 ng/ml) of CEA are associated with worse prognosis than are low concentrations. Further, some studies in the literature report that slow rising CEA levels indicates local recurrence while rapidly increasing levels suggests
10 hepatic metastasis.

Lung Cancer

Examples of serum markers useful in the present invention to monitor lung cancer therapy include, but are not limited to, CEA, cytokeratin 19 fragments (CYFRA
15 21-1), and Neuron Specific Enolase (NSE).

NSE is a glycolytic isoenzyme of enolase produced in central and peripheral neurons and malignant tumors of neuroectodermal origin. At diagnosis, NSE concentrations greater than 25 ng/mL are suggestive of
20 malignancy and lung cancer while concentrations greater than 100 ng/mL are suggestive of small cell lung cancer.

CYFRA 21-1 is a tumor marker test which uses two specific monoclonal antibodies against a cytokeratin 19 fragment. At diagnosis, CYFRA 21-1 concentrations
25 greater than 10 ng/mL are suggestive of malignancy while concentrations greater than 30 ng/mL are suggestive of lung cancer.

Accordingly, dosing of the cyclooxygenase-2 inhibitor, matrix metalloproteinase inhibitor, and
30 antineoplastic agent may be determined and adjusted based on measurement of tumor markers in body fluids or

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tissues, particularly based on tumor markers in serum. For example, a decrease in serum marker level relative to baseline serum marker prior to administration of the matrix metalloproteinase inhibitor, cyclooxygenase-2 inhibitor and antineoplastic agent indicates a decrease in cancer-associated changes and provides a correlation with inhibition of the cancer. In one embodiment, therefore, the method of the present invention comprises administering the cyclooxygenase-2 inhibitor, matrix metalloproteinase inhibitor, and antineoplastic agent at doses that in combination result in a decrease in one or more tumor markers, particularly a decrease in one or more serum tumor markers, in the mammal relative to baseline tumor marker levels.

Similarly, the rate of postoperative decrease of a particular marker predicts patient outcome. Decreasing tumor marker concentrations and half lives after surgery indicates a good prognosis, while tumor marker concentrations which decline slowly and don't reach the normal reference range predict residual tumor and poor prognosis. Further, during follow-up therapy, increases in tumor marker concentration predicts recurrent disease many months before clinical manifestation.

In addition to the above examples, Table No. 4, below, lists several references, hereby individually incorporated by reference herein, that describes tumor markers and their use in detecting and monitoring tumor growth and progression.

Table No. 4. Tumor marker references.

| |
|--|
| European Group on Tumor Markers Publications |
|--|

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Committee. Consensus Recommendations. Anticancer Research 19: 2785-2820 (1999)

Human Cytogenetic Cancer Markers. Sandra R. Wolman and Stewart Sell (eds.). Totowa, New Jersey: Humana Press. 1997

Cellular Markers of Cancer. Carleton Garrett and Stewart Sell (eds.). Totowa, New Jersey: Human Press. 1995

Combinations with Other Treatments

5 The COX- 2 inhibitors and MMP inhibitors of the present invention may be used in conjunction with other treatment modalities, including, but not limited to surgery and radiation, hormonal therapy, chemotherapy, immunotherapy, and cryotherapy. The present invention may be used in conjunction with any current or future therapy.

10 The following discussion highlights some agents in this respect, which are illustrative, not limitative. A wide variety of other effective agents also may be used.

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Surgery and Radiation

In general, surgery and radiation therapy are employed as potentially curative therapies for patients under 70 years of age who present with clinically
5 localized disease and are expected to live at least 10 years.

For example, approximately 70% of newly diagnosed prostate cancer patients fall into this category. Approximately 90% of these patients (65% of total
10 patients) undergo surgery, while approximately 10% of these patients (7% of total patients) undergo radiation therapy. Histopathological examination of surgical specimens reveals that approximately 63% of patients undergoing surgery (40% of total patients) have locally
15 extensive tumors or regional (lymph node) metastasis that was undetected at initial diagnosis. These patients are at a significantly greater risk of recurrence. Approximately 40% of these patients will actually develop recurrence within five years after surgery.
20 Results after radiation are even less encouraging. Approximately 80% of patients who have undergone radiation as their primary therapy have disease persistence or develop recurrence or metastasis within five years after treatment. Currently, most of these
25 surgical and radiotherapy patients generally do not receive any immediate follow-up therapy. Rather, for example, they are monitored frequently for elevated Prostate Specific Antigen ("PSA"), which is the primary indicator of recurrence or metastasis prostate cancer.
30 Thus, there is considerable opportunity to use the present invention in conjunction with surgical intervention.

Hormonal Therapy

Hormonal ablation is the most effective palliative treatment for the 10% of patients presenting with metastatic prostate cancer at initial diagnosis. Hormonal ablation by medication and/or orchiectomy is used to block hormones that support the further growth and metastasis of prostate cancer. With time, both the primary and metastatic tumors of virtually all of these patients become hormone-independent and resistant to therapy. Approximately 50% of patients presenting with metastatic disease die within three years after initial diagnosis, and 75% of such patients die within five years after diagnosis. Continuous supplementation with NAALADase inhibitor based drugs are used to prevent or reverse this potentially metastasis-permissive state.

Among hormones which may be used in combination with the present inventive compounds, diethylstilbestrol (DES), leuprolide, flutamide, cyproterone acetate, ketoconazole and amino glutethimide are preferred.

Immunotherapy

The COX-2 inhibitors and MMP inhibitors of the present invention may also be used in combination with monoclonal antibodies in treating cancer. For example monoclonal antibodies may be used in treating prostate cancer. A specific example of such an antibody includes cell membrane-specific anti-prostate antibody.

The present invention may also be used with immunotherapies based on polyclonal or monoclonal antibody-derived reagents, for instance. Monoclonal antibody-based reagents are most preferred in this

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regard. Such reagents are well known to persons of ordinary skill in the art. Radiolabelled monoclonal antibodies for cancer therapy, such as the recently approved use of monoclonal antibody conjugated with
5 strontium-89, also are well known to persons of ordinary skill in the art.

Antiangiogenic Therapy

The COX-2 inhibitors and MMP inhibitors may also be
10 used in combination with other antiangiogenic agent in treating cancer. Antiangiogenic agents include but are not limited to MMP inhibitors, integrin antagonists, angiostatin, endostatin, thrombospondin-1, and interferon alpha. Examples of preferred antiangiogenic
15 agents include, but are not limited to vitaxin, marimastat, Bay-12-9566, AG-3340, metastat, celecoxib, rofecoxib, JTE-522, EMD-121974, and D-2163 (BMS-275291).

Cryotherapy

20 Cryotherapy recently has been applied to the treatment of some cancers. Methods and compositions of the present invention also could be used in conjunction with an effective therapy of this type.

25 All of the various cell types of the body can be transformed into benign or malignant neoplasia or tumor cells and are contemplated as objects of the invention. A "benign" tumor cell denotes the non-invasive and non-metastasized state of a neoplasm. In man the most
30 frequent neoplasia site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia,

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central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer. Examples 1 through 9 are provided to illustrate contemplated therapeutic combinations, and
5 are not intended to limit the scope of the invention.

Illustrations

The following non-limiting illustrative examples describe various cancer diseases and therapeutic
10 approaches that may be used in the present invention, and are for illustrative purposes only. Preferred antiangiogenic agents of the below non-limiting illustrations are MMP inhibitors and COX-2 inhibitors. More preferably the MMP inhibitors include Compound M1,
15 Compound M2, Compound M3, Compound M4, Compound M5, Compound M6, Compound M7, Compound M8, Marimastat, Bay-12-9566, AG-3340, Metastat, and D-2163 (BMS-275291) and the COX-2 inhibitors include celecoxib, rofecoxib and JTE-522.

20

Example 1

Lung Cancer

In many countries including Japan, Europe and
25 America, the number of patients with lung cancer is fairly large and continues to increase year after year and is the most frequent cause of cancer death in both men and women. Although there are many potential causes for lung cancer, tobacco use, and particularly cigarette
30 smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in smokers, or radon are contributory factors. Also

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occupational hazards such as exposure to uranium have been identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of cancer.

5 Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell lung cancer (oat cell). Non-small cell lung cancer
10 (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell lung cancer (SCLC). Thus, chemotherapeutic formulas and radiation therapy are different between these two types of lung cancer.

15

Non-Small Cell Lung Cancer

Where the location of the non-small cell lung cancer tumor can be easily excised (stage I and II disease) surgery is the first line of therapy and offers
20 a relatively good chance for a cure. However, in more advanced disease (stage IIIa and greater), where the tumor has extended to tissue beyond the bronchopulmonary lymph nodes, surgery may not lead to complete excision of the tumor. In such cases, the patient's chance for a
25 cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC tumor, other types of therapies must be utilized.

Today radiation therapy is the standard treatment to control unresectable or inoperable NSCLC. Improved
30 results have been seen when radiation therapy has been combined with chemotherapy, but gains have been modest

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and the search continues for improved methods of combining modalities.

Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration but the two most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. A preferred course of treatment for a patient undergoing radiation therapy for NSCLC will be a treatment schedule over a 5 to 6 week period, with a total dose of 50 to 60 Gy administered to the patient in a single daily fraction of 1.8 to 2.0 Gy, 5 days a week. A Gy is an abbreviation for Gray and refers to 100 rad of dose.

However, as NSCLC is a systemic disease, and radiation therapy is a local modality, radiation therapy as a single line of therapy is unlikely to provide a cure for NSCLC, at least for those tumors that have metastasized distantly outside the zone of treatment. Thus, the use of radiation therapy with other modality regimens have important beneficial effects for the treatment of NSCLC.

Generally, radiation therapy has been combined temporally with chemotherapy to improve the outcome of treatment. There are various terms to describe the temporal relationship of administering radiation therapy

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in combination with MMP inhibitors and COX-2 inhibitors and/or chemotherapy, and the following examples are the preferred treatment regimens and are provided for illustration only and are not intended to limit the use of other combinations. "Sequential" therapy refers to the administration of chemotherapy and/or MMP inhibitors and/or COX-2 inhibitors and/or radiation therapy separately in time in order to allow the separate administration of either chemotherapy and/or MMP inhibitors and/or COX-2 inhibitors, and/or radiation therapy. "Concomitant" therapy refers to the administration of chemotherapy and/or MMP inhibitors, and/or COX-2 inhibitors and/or radiation therapy on the same day. Finally, "alternating therapy" refers to the administration of radiation therapy on the days in which chemotherapy and/or MMP inhibitors and/or COX-2 inhibitors would not have been administered if it was given alone.

It is reported that advanced non-small cell lung cancers do not respond favorably to single-agent chemotherapy and useful therapies for advanced inoperable cancers have been limited. (Journal of Clinical Oncology, vol. 10, pp. 829-838 (1992)).

Japanese Patent Kokai 5-163293 refers to some specified antibiotics of 16-membered-ring macrolides as a drug delivery carrier capable of transporting anthracycline-type anticancer drugs into the lungs for the treatment of lung cancers. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell lung cancers.

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WO 93/18,652 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell lung cancers, but they have not yet been clinically
5 practicable.

Pharmacology, vol. 41, pp. 177-183 (1990) describes that a long-term use of erythromycin increases productions of interleukins 1, 2 and 4, all of which contribute to host immune responses, but there is no
10 reference to the effect of this drug on non-small cell lung cancers.

Teratogenesis, Carcinogenesis, and Mutagenesis, vol. 10, pp. 477-501 (1990) describes that some of antimicrobial drugs can be used as an anticancer agent,
15 but does not refer to their application to non-small cell lung cancers.

In addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell lung cancers.

20 Any 14 - or 15-membered-ring macrolides have not been reported to be effective against non-small cell lung cancers.

However, several chemotherapeutic agents have been shown to be efficacious against NSCLC. Preferred
25 chemotherapeutic agents that can be used in the present invention against NSCLC include etoposide, carboplatin, methotrexate, 5-Fluorouracil, epirubicin, doxorubicin, taxol, inhibitor of normal mitotic activity; and cyclophosphamide. Even more preferred chemotherapeutic
30 agents active against NSCLC include cisplatin, ifosfamide, mitomycin C, epirubicin, vinblastine, and vindesine.

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Other agents that are under investigation for use against NSCLC include: camptothecins, a topoisomerase 1 inhibitor; navelbine (vinorelbine), a microtubule assembly inhibitor; gemcitabine, a deoxycytidine analogue; fotemustine, a nitrosourea compound; and edatrexate, a antifol.

The overall and complete response rates for NSCLC has been shown to increase with use of combination chemotherapy as compared to single-agent treatment.

10 Haskel CM: Chest. 99: 1325, 1991; Bakowski MT: Cancer Treat Rev 10:159, 1983; Joss RA: Cancer Treat Rev 11:205, 1984.

A preferred therapy for the treatment of NSCLC is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) ifosfamide, cisplatin, etoposide; 2) cyclophosphamide, doxorubicin, cisplatin; 3) ifosfamide, carboplatin, etoposide; 4) bleomycin, etoposide, cisplatin; 5) ifosfamide, mitomycin, cisplatin; 6) cisplatin, vinblastine; 7) cisplatin, vindesine; 8) mitomycin C, vinblastine, cisplatin; 9) mitomycin C, vindesine, cisplatin; 10) ifosfamide, etoposide; 11) etoposide, cisplatin; 12) ifosfamide, mitomycin C; 13) fluorouracil, cisplatin, vinblastine; 14) carboplatin, etoposide; or radiation therapy.

Accordingly, apart from the conventional concept of anticancer therapy, there is a strong need for the development of therapies practicably effective for the treatment of non-small cell lung cancers.

Small Cell Lung Cancer

Approximately 15 to 20 percent of all cases of lung cancer reported worldwide is small cell lung cancer (SCLC). Ihde DC: Cancer 54:2722, 1984. Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy, radiation therapy and surgery. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary tumor and persistence of the tumor in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

A preferred therapy for the treatment of lung cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following antineoplastic agents: vincristine, cisplatin, carboplatin, cyclophosphamide, epirubicin (high dose), etoposide (VP-16) I.V., etoposide (VP-16) oral, isofamide, teniposide (VM-26), and doxorubicin. Other preferred single-agents chemotherapeutic agents that may be used in the present invention include BCNU (carmustine), vindesine, hexamethylmelamine (altretamine), methotrexate, nitrogen mustard, and CCNU (lomustine). Other chemotherapeutic agents under investigation that have shown activity againe SCLC include iroplatin, gemcitabine, lonidamine, and taxol. Single-agent chemotherapeutic agents that have not shown activity against SCLC include mitoguazone, mitomycin C, aclarubicin, diaziquone, bisantrene, cytarabine, idarubicin, mitomxantrone, vinblastine, PCNU and esorubicin.

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The poor results reported from single-agent chemotherapy has led to use of combination chemotherapy.

A preferred therapy for the treatment of NSCLC is a combination of therapeutically effective amounts of one
5 or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) etoposide (VP-16), cisplatin; 2) cyclophosphamide, adriamycin [(doxorubicin), vincristine, etoposide (VP-16)]; 3) Cyclophosphamide,
10 adriamycin(doxorubicin), vincristine; 4) Etoposide (VP-16), ifosfamide, cisplatin; 5) etoposide (VP-16), carboplatin; 6) cisplatin, vincristine (Oncovin), doxorubicin, etoposide.

Additionally, radiation therapy in conjunction with
15 the preferred combinations of COX-2 inhibitors and MMP inhibitors and systemic chemotherapy is contemplated to be effective at increasing the response rate for SCLC patients. The typical dosage regimen for radiation therapy ranges from 40 to 55 Gy, in 15 to 30 fractions,
20 3 to 7 times week. The tissue volume to be irradiated is determined by several factors and generally the hilum and subcarinal nodes, and bilateral mediastinal nodes up to the thoracic inlet are treated, as well as the primary tumor up to 1.5 to 2.0 cm of the margins.

25

Example 2

Colorectal Cancer

Survival from colorectal cancer depends on the
30 stage and grade of the tumor, for example precursor adenomas to metastatic adenocarcinoma. Generally, colorectal cancer can be treated by surgically removing

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the tumor, but overall survival rates remain between 45 and 60 percent. Colonic excision morbidity rates are fairly low and is generally associated with the anastomosis and not the extent of the removal of the tumor and local tissue. In patients with a high risk of reoccurrence, however, chemotherapy has been incorporated into the treatment regimen in order to improve survival rates.

Tumor metastasis prior to surgery is generally believed to be the cause of surgical intervention failure and up to one year of chemotherapy is required to kill the non-excised tumor cells. As severe toxicity is associated with the chemotherapeutic agents, only patients at high risk of recurrence are placed on chemotherapy following surgery. Thus, the incorporation of an antiangiogenesis inhibitor into the management of colorectal cancer will play an important role in the treatment of colorectal cancer and lead to overall improved survival rates for patients diagnosed with colorectal cancer.

A preferred combination therapy for the treatment of colorectal cancer is surgery, followed by a regimen of one or more chemotherapeutic agents and an MMP inhibitor and a COX-2 inhibitor cycled over a one year time period. A more preferred combination therapy for the treatment of colorectal cancer is a regimen of one or more MMP inhibitors and/or COX-2 inhibitors, followed by surgical removal of the tumor from the colon or rectum and then followed by a regimen of one or more chemotherapeutic agents and one or more antiangiogenic agents, cycled over a one year time period. An even more preferred therapy for the treatment of colon cancer is a

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combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

A more preferred therapy for the treatment of colon cancer is a combination of therapeutically effective
5 amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following antineoplastic agents: fluorouracil, and Levamisole. Preferably, fluorouracil and Levamisole are used in combination.

10

Example 3

Breast Cancer

Today, among women in the United States, breast
15 cancer remains the most frequent diagnosed cancer. One in 8 women in the United States are at risk of developing breast cancer in their lifetime. Age, family history, diet, and genetic factors have been identified as risk factors for breast cancer. Breast cancer is the
20 second leading cause of death among women.

Different chemotherapeutic agents are known in art for treating breast cancer. Cytotoxic agents used for treating breast cancer include
doxorubicin, cyclophosphamide, methotrexate, 5-
25 fluorouracil, mitomycin C, mitoxantrone, taxol, and epirubicin. CANCER SURVEYS, Breast Cancer volume 18, Cold Spring Harbor Laboratory Press, 1993.

In the treatment of locally advanced noninflammatory breast cancer, MMP inhibitors and/or
30 COX-2 inhibitors can be used to treat the disease in combination with other COX-2 inhibitors, other MMP inhibitors, antiangiogenic agents, or in combination

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with surgery, radiation therapy or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, radiation therapy and surgery that can be used in combination with the present invention include, but

5 are not limited to the following combinations: 1) doxorubicin, vincristine, radical mastectomy; 2) doxorubicin, vincristine, radiation therapy; 3) cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone, mastectomy; 4) cyclophosphamide,

10 doxorubicin, 5-flourouracil, vincristine, prednisone, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, radiation therapy for pathologic complete response; 6) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen,

15 mastectomy, radiation therapy for pathologic partial response; 7) mastectomy, radiation therapy, levamisole; 8) mastectomy, radiation therapy; 9) mastectomy, vincristine, doxorubicin, cyclophosphamide, levamisole; 10) mastectomy, vincristine, doxorubicin,

20 cyclophosphamide; 11) mastectomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin, radiation therapy; 12) mastectomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin.

In the treatment of locally advanced inflammatory

25 breast cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery, radiation therapy or with chemotherapeutic agents.

30 Preferred combinations of chemotherapeutic agents, radiation therapy and surgery that can be used in combination with the present invention include, but or

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not limited to the following combinations: 1) cyclophosphamide, doxorubicin, 5-fluorouracil, radiation therapy; 2) cyclophosphamide, doxorubicin, 5-fluorouracil, mastectomy, radiation therapy; 3) 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, prednisone, mastectomy, radiation therapy; 4) 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, mastectomy, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, radiation therapy; 6) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, mastectomy, radiation therapy; 7) doxorubicin, vincristine, methotrexate, radiation therapy, followed by vincristine, cyclophosphamide, 5-fluorouracil; 8) doxorubicin, vincristine, cyclophosphamide, methotrexate, 5-fluorouracil, radiation therapy, followed by vincristine, cyclophosphamide, 5-fluorouracil; 9) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 10) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 11) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine, tamoxifen;; 12) surgery, followed by cyclophosphamide, methotrexate, 5-

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fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine; 13) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 14) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine; 15) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine; 16) 5-fluorouracil, doxorubicin, cyclophosphamide followed by mastectomy, followed by 5-fluorouracil, doxorubicin, cyclophosphamide, followed by radiation therapy.

In the treatment of metastatic breast cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery, radiation therapy or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents that can be used in combination with the angiogenesis inhibitors of the present invention include, but are not limited to the following combinations: 1) cyclophosphamide, methotrexate, 5-fluorouracil; 2) cyclophosphamide, adriamycin, 5-fluorouracil; 3) cyclophosphamide, methotrexate, 5-

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flurouracil, vincristine, prednisone; 4) adriamycin, vincristine; 5) thiotepa, adriamycin, vinblastine; 6) mitomycin, vinblastine; 7) cisplatin, etoposide.

5 Example 4

Prostate Cancer

Prostate cancer is now the leading form of cancer among men and the second most frequent cause of death
10 from cancer in men. It is estimated that more than 165,000 new cases of prostate cancer were diagnosed in 1993, and more than 35,000 men died from prostate cancer in that year. Additionally, the incidence of prostate cancer has increased by 50% since 1981, and mortality
15 from this disease has continued to increase. Previously, most men died of other illnesses or diseases before dying from their prostate cancer. We now face increasing morbidity from prostate cancer as men live longer and the disease has the opportunity to progress.

20 Current therapies for prostate cancer focus exclusively upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. In addition to the use of digital rectal examination and transrectal ultrasonography, prostate-specific antigen
25 (PSA) concentration is frequently used in the diagnosis of prostate cancer.

A preferred therapy for the treatment of prostate cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2
30 inhibitors.

U.S. Pat. No. 4,472,382 discloses treatment of benign

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prostatic hyperplasia (BPH) with an antiandrogen and certain peptides which act as LH-RH agonists.

U.S. Pat. No. 4,596,797 discloses aromatase inhibitors as a method of prophylaxis and/or treatment
5 of prostatic hyperplasia.

U.S. Pat. No. 4,760,053 describes a treatment of certain cancers which combines an LHRH agonist with an antiandrogen and/or an antiestrogen and/or at least one inhibitor of sex steroid biosynthesis.

10 U.S. Pat. No. 4,775,660 discloses a method of treating breast cancer with a combination therapy which may include surgical or chemical prevention of ovarian secretions and administering an antiandrogen and an antiestrogen.

15 U.S. Pat. No. 4,659,695 discloses a method of treatment of prostate cancer in susceptible male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g. by use of an LHRH agonist, which comprises administering an
20 antiandrogen, e.g. flutamide, in association with at least one inhibitor of sex steroid biosynthesis, e.g. aminoglutethimide and/or ketoconazole.

Prostate Specific Antigen

25 One well known prostate cancer marker is Prostate Specific Antigen (PSA). PSA is a protein produced by prostate cells and is frequently present at elevated levels in the blood of men who have prostate cancer. PSA has been shown to correlate with tumor burden, serve as
30 an indicator of metastatic involvement, and provide a parameter for following the response to surgery, irradiation, and androgen replacement therapy in

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prostate cancer patients. It should be noted that Prostate Specific Antigen (PSA) is a completely different protein from Prostate Specific Membrane Antigen (PSMA). The two proteins have different
5 structures and functions and should not be confused because of their similar nomenclature.

Prostate Specific Membrane Antigen (PSMA)

In 1993, the molecular cloning of a prostate-specific membrane antigen (PSMA) was reported as a
10 potential prostate carcinoma marker and hypothesized to serve as a target for imaging and cytotoxic treatment modalities for prostate cancer. Antibodies against PSMA have been described and examined clinically for
15 diagnosis and treatment of prostate cancer. In particular, Indium-111 labelled PSMA antibodies have been described and examined for diagnosis of prostate cancer and itrium-labelled PSMA antibodies have been described and examined for the treatment of prostate
20 cancer.

Example 5

Bladder Cancer

25 The classification of bladder cancer is divided into three main classes: 1) superficial disease, 2) muscle-invasive disease, and 3) metastatic disease.

Currently, transurethral resection (TUR), or segmental resection, account for first line therapy of
30 superficial bladder cancer, i.e., disease confined to the mucosa or the lamina propria. However, intravesical therapies are necessary, for example, for the treatment

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of high-grade tumors, carcinoma in situ, incomplete resections, recurrences, and multifocal papillary. Recurrence rates range from up to 30 to 80 percent, depending on stage of cancer.

5 Therapies that are currently used as intravesical therapies include chemotherapy, immunotherapy, bacille Calmette-Guerin (BCG) and photodynamic therapy. The main objective of intravesical therapy is twofold: to prevent recurrence in high-risk patients and to treat
10 disease that cannot be resected. The use of intravesical therapies must be balanced with its potentially toxic side effects. Additionally, BCG requires an unimpaired immune system to induce an antitumor effect. Chemotherapeutic agents that are
15 known to be inactive against superficial bladder cancer include Cisplatin, actinomycin D, 5-fluorouracil, bleomycin, and cyclophosphamide methotrexate.

In the treatment of superficial bladder cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat
20 the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in combination with surgery (TUR), chemotherapy and intravesical therapies.

A preferred therapy for the treatment of
25 superficial bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with: thiotepa (30 to 60 mg/day), mitomycin C (20 to 60 mg/day), and doxorubicin (20 to 80 mg/day).

30 A preferred intravesicle immunotherapeutic agent that may be used in the present invention is BCG. A preferred daily dose ranges from 60 to 120 mg, depending

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on the strain of the live attenuated tuberculosis organism used.

A preferred photodynamic therapeutic agent that may be used with the present invention is Photofrin I, a
5 photosensitizing agent, administered intravenously. It is taken up by the low-density lipoprotein receptors of the tumor cells and is activated by exposure to visible light. Additionally, neodymium YAG laser activation generates large amounts of cytotoxic free radicals and
10 singlet oxygen.

In the treatment of muscle-invasive bladder cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP
inhibitors and/or COX-2 inhibitors, antiangiogenic
15 agents, or in combination with surgery (TUR), intravesical chemotherapy, radiation therapy, and radical cystectomy with pelvic lymph node dissection.

A preferred radiation dose for the treatment of bladder cancer is between 5,000 to 7,000 cGY in
20 fractions of 180 to 200 cGY to the tumor. Additionally, 3,500 to 4,700 cGY total dose is administered to the normal bladder and pelvic contents in a four-field technique. Radiation therapy should be considered only if the patient is not a surgical candidate, but may be
25 considered as preoperative therapy.

A preferred combination of surgery and chemotherapeutic agents that can be used in combination with the MMP inhibitors and/or COX-2 inhibitors of the present invention is cystectomy in conjunction with five
30 cycles of cisplatin (70 to 100 mg/m²); doxorubicin (50 to 60 mg/m²); and cyclophosphamide (500 to 600 mg/m²).

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A more preferred therapy for the treatment of superficial bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

5 An even more preferred combination for the treatment of superficial bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1)
10 cisplatin, doxorubicin, cyclophosphamide; and 2) cisplatin, 5-fluorouracil. An even more preferred combination of chemotherapeutic agents that can be used in combination with radiation therapy and the , MMP inhibitors and/or COX-2 inhibitors is a combination of
15 cisplatin, methotrexate, vinblastine.

Currently no curative therapy exists for metastatic bladder cancer. The present invention contemplates an effective treatment of bladder cancer leading to improved tumor inhibition or regression, as compared to
20 current therapies.

In the treatment of metastatic bladder cancer, MMP inhibitors and/or COX-2 inhibitors can be used to treat the disease in combination with other MMP inhibitors and/or COX-2 inhibitors, antiangiogenic agents, or in
25 combination with surgery, radiation therapy or with chemotherapeutic agents.

A preferred therapy for the treatment of metastatic bladder cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or
30 COX-2 inhibitors.

A more preferred combination for the treatment of metastatic bladder cancer is a combination of

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therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) cisplatin and methotrexate; 2) doxorubicin, vinblastine, cyclophosphamide, and 5-fluorouracil; 3) vinblastine, doxorubicin, cisplatin, methotrexate; 4) vinblastine, cisplatin, methotrexate; 5) cyclophosphamide, doxorubicin, cisplatin; 6) 5-fluorouracil, cisplatin.

10 Example 6

Pancreas Cancer

Approximately 2% of new cancer cases diagnoses in the United States is pancreatic cancer. Pancreatic cancer is generally classified into two clinical types: 1) adenocarcinoma (metastatic and non-metastatic), and 2) cystic neoplasms (serous cystadenomas, mucinous cystic neoplasms, papillary cystic neoplasms, acinar cell cystadenocarcinoma, cystic choriocarcinoma, cystic teratomas, angiomatous neoplasms).

Preferred combinations of therapy for the treatment of non-metastatic adenocarcinoma that may be used in the present invention include the use of MMP inhibitors and/or COX-2 inhibitors along with preoperative biliary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant radiation; and chemotherapy.

For the treatment of metastatic adenocarcinoma, a preferred combination therapy consists of an antiangiogenesis inhibitor of the present invention in

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combination with continuous treatment of 5-fluorouracil, followed by weekly cisplatin therapy.

A more preferred combination therapy for the treatment of cystic neoplasms is the use of MMP inhibitors and/or COX-2 inhibitors along with resection.

Example 7

Ovary Cancer

10 Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. A preferred therapy for the treatment of ovary cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

15 Preferred single agents that can be used in combination with an antiangiogenesis agent include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, 20 hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gama.

Preferred combinations for the treatment of celomic epithelial carcinoma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamethylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) 25 cyclophosphamide, hexamethylmelamine, 5-fluorouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, 30

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cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethylmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

10 Germ cell ovarian cancer accounts for approximately 5% of ovarian cancer cases. Germ cell ovarian carcinomas are classified into two main groups: 1) dysgerminoma, and nondysgerminoma. Nondysgerminoma is further classified into teratoma, endodermal sinus
15 tumor, embryonal carcinoma, chloricarcinoma, polyembryoma, and mixed cell tumors.

A preferred therapy for the treatment of germ cell carcinoma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2
20 inhibitors.

A more preferred therapy for the treatment of germ cell carcinoma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following
25 combinations of antineoplastic agents: 1) vincristine, actinomycin D, cyclophosphamide; 2) bleomycin, etoposide, cisplatin; 3) vinblastine, bleomycin, cisplatin.

Cancer of the fallopian tube is the least common
30 type of ovarian cancer, accounting for approximately 400 new cancer cases per year in the United States. Papillary serous adenocarcinoma accounts for

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approximately 90% of all malignancies of the ovarian tube.

A preferred therapy for the treatment of fallopian tube cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors.

A more preferred therapy for the treatment of fallopian tube cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gama.

An even more preferred therapy for the treatment of fallopian tube cancer is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamethylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamethylmelamine, 5-fluorouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11)

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cyclophosphamide, hexamethylmelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

5 Example 8

Central Nervous System Cancers

Central nervous system cancer accounts for approximately 2% of new cancer cases in the United States. Common intracranial neoplasms include glioma, 10 meningioma, neurinoma, and adenoma.

A preferred therapy for the treatment of central nervous system cancers is a combination of therapeutically effective amounts of one or more MMP 15 inhibitors and/or COX-2 inhibitors.

A preferred therapy for the treatment of malignant glioma is a combination of therapeutically effective amounts of one or more MMP inhibitors and/or COX-2 inhibitors in combination with the following 20 combinations of therapies and antineoplastic agents: 1) radiation therapy, BCNU (carmustine); 2) radiation therapy, methyl CCNU (lomustine); 3) radiation therapy, medrol; 4) radiation therapy, procarbazine; 5) radiation therapy, BCNU, medrol; 6) hyperfraction radiation 25 therapy, BCNU; 7) radiation therapy, misonidazole, BCNU; 8) radiation therapy, streptozotocin; 9) radiation therapy, BCNU, procarbazine; 10) radiation therapy, BCNU, hydroxyurea, procarbazine, VM-26; 11) radiation therapy, BNCU, 5-fluorouracil; 12) radiation therapy, 30 Methyl CCNU, dacarbazine; 13) radiation therapy, misonidazole, BCNU; 14) diaziquone; 15) radiation therapy, PCNU; 16) procarbazine (matulane), CCNU,

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vincristine. A preferred dose of radiation therapy is about 5,500 to about 6,000 cGY. Preferred radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR). It is also contemplated that radiosurgery may be used in combinations with antiangiogenesis agents.

Example 9

Additional examples of combinations are listed in Table No 22.

Table No. 22. Therapy Combinations

| COX-2 Inhibitor | MMP Inhibitor |
|------------------------|----------------------|
| Celecoxib | Compound M1 |
| Celecoxib | Compound M2 |
| Celecoxib | Compound M3 |
| Celecoxib | Compound M4 |
| Celecoxib | Compound M5 |
| Celecoxib | Compound M7 |
| Celecoxib | Bay-12-9566 |
| Celecoxib | Metastat |
| Celecoxib | D-2163 |
| Celecoxib | D-1927 |
| Rofecoxib | Compound M1 |
| Rofecoxib | Compound M2 |
| Rofecoxib | Compound M3 |
| Rofecoxib | Compound M4 |
| Rofecoxib | Compound M5 |
| Rofecoxib | Compound M7 |
| Rofecoxib | Marimastat |

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| | |
|-----------|-------------|
| Rofecoxib | Bay-12-9566 |
| Rofecoxib | AG-3340 |
| Rofecoxib | Metastat |
| Rofecoxib | D-2163 |
| Rofecoxib | D-1927 |
| JTE-522 | Compound M1 |
| JTE-522 | Compound M2 |
| JTE-522 | Compound M3 |
| JTE-522 | Compound M4 |
| JTE-522 | Compound M5 |
| JTE-522 | Compound M7 |
| JTE-522 | Marimastat |
| JTE-522 | Bay-12-9566 |
| JTE-522 | AG-3340 |
| JTE-522 | Metastat |
| JTE-522 | D-2163 |
| JTE-522 | D-1927 |

Further additional examples of combinations are listed in Table No 23.

5 **Table No. 23. Additional examples of combination therapies**

| COX-2 Inhibitor | MMP Inhibitor | Antineoplastic Agent | Indication |
|----------------------------|--------------------------|---------------------------------|---------------------|
| Celecoxib | Compound M1 | Anastrozole | Breast |
| Celecoxib | Compound M1 | Capecitabine | Breast |
| Celecoxib | Compound M1 | Docetaxel | Breast |
| Celecoxib | Compound M1 | Gemcitabine | Breast, Pancreas |
| Celecoxib | Compound M1 | Letrozole | Breast |

| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M1 | Megestrol | Breast |
| Celecoxib | Compound M1 | Paclitaxel | Breast |
| Celecoxib | Compound M1 | Tamoxifen | Breast |
| Celecoxib | Compound M1 | Toremifene | Breast |
| Celecoxib | Compound M1 | Vinorelbine | Breast, Lung |
| Celecoxib | Compound M1 | Topotecan | Lung |
| Celecoxib | Compound M1 | Etoposide | Lung |
| Celecoxib | Compound M1 | Fluorouracil | Colon |
| Celecoxib | Compound M1 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Compound M1 | Retinoids | Colon |
| Celecoxib | Compound M1 | DFMO | Colon |
| Celecoxib | Compound M1 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M1 | calcium carbonate | Colon |
| Celecoxib | Compound M1 | selenium | Colon |
| Celecoxib | Compound M1 | sulindac sulfone | Colon |
| Celecoxib | Compound M1 | Carboplatin | Brain |
| Celecoxib | Compound M1 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M1 | Ketoconazole | Prostate |
| Celecoxib | Compound M1 | Cisplatin | |
| Celecoxib | Compound M2 | Anastrozole | Breast |
| Celecoxib | Compound M2 | Capecitabine | Breast |
| Celecoxib | Compound M2 | Docetaxel | Breast |
| Celecoxib | Compound M2 | Gemcitabine | Breast, Pancreas |
| Celecoxib | Compound M2 | Letrozole | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M2 | Megestrol | Breast |
| Celecoxib | Compound M2 | Paclitaxel | Breast |
| Celecoxib | Compound M2 | Tamoxifen | Breast |
| Celecoxib | Compound M2 | Toremifene | Breast |
| Celecoxib | Compound M2 | Vinorelbine | Breast, Lung |
| Celecoxib | Compound M2 | Topotecan | Lung |
| Celecoxib | Compound M2 | Etoposide | Lung |
| Celecoxib | Compound M2 | Fluorouracil | Colon |
| Celecoxib | Compound M2 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Compound M2 | Retinoids | Colon |
| Celecoxib | Compound M2 | DFMO | Colon |
| Celecoxib | Compound M2 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M2 | calcium carbonate | Colon |
| Celecoxib | Compound M2 | selenium | Colon |
| Celecoxib | Compound M2 | sulindac sulfone | Colon |
| Celecoxib | Compound M2 | Carboplatin | Brain |
| Celecoxib | Compound M2 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M2 | Ketoconazole | Prostate |
| Celecoxib | Compound M2 | Cisplatin | |
| Celecoxib | Compound M3 | Anastrozole | Breast |
| Celecoxib | Compound M3 | Capecitabine | Breast |
| Celecoxib | Compound M3 | Docetaxel | Breast |
| Celecoxib | Compound M3 | Gemcitabine | Breast, Pancreas |
| Celecoxib | Compound M3 | Letrozole | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M3 | Megestrol | Breast |
| Celecoxib | Compound M3 | Paclitaxel | Breast |
| Celecoxib | Compound M3 | Tamoxifen | Breast |
| Celecoxib | Compound M3 | Toremifene | Breast |
| Celecoxib | Compound M3 | Vinorelbine | Breast, Lung |
| Celecoxib | Compound M3 | Topotecan | Lung |
| Celecoxib | Compound M3 | Etoposide | Lung |
| Celecoxib | Compound M3 | Fluorouracil | Colon |
| Celecoxib | Compound M3 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Compound M3 | Retinoids | Colon |
| Celecoxib | Compound M3 | DFMO | Colon |
| Celecoxib | Compound M3 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M3 | calcium carbonate | Colon |
| Celecoxib | Compound M3 | selenium | Colon |
| Celecoxib | Compound M3 | sulindac sulfone | Colon |
| Celecoxib | Compound M3 | Carboplatin | Brain |
| Celecoxib | Compound M3 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M3 | Ketoconazole | Prostate |
| Celecoxib | Compound M3 | Cisplatin | |
| Celecoxib | Compound M4 | Anastrozole | Breast |
| Celecoxib | Compound M4 | Capecitabine | Breast |
| Celecoxib | Compound M4 | Docetaxel | Breast, Pancreas |
| Celecoxib | Compound M4 | Gemcitabine | Breast |
| Celecoxib | Compound M4 | Letrozole | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M4 | Megestrol | Breast |
| Celecoxib | Compound M4 | Paclitaxel | Breast |
| Celecoxib | Compound M4 | Tamoxifen | Breast |
| Celecoxib | Compound M4 | Toremifene | Breast, Lung |
| Celecoxib | Compound M4 | Vinorelbine | Lung |
| Celecoxib | Compound M4 | Topotecan | Lung |
| Celecoxib | Compound M4 | Etoposide | Colon |
| Celecoxib | Compound M4 | Fluorouracil | Colon, Bladder |
| Celecoxib | Compound M4 | Irinotecan (CPT-11) | Colon |
| Celecoxib | Compound M4 | Retinoids | Colon |
| Celecoxib | Compound M4 | DFMO | Colon |
| Celecoxib | Compound M4 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M4 | calcium carbonate | Colon |
| Celecoxib | Compound M4 | selenium | Colon |
| Celecoxib | Compound M4 | sulindac sulfone | Colon |
| Celecoxib | Compound M4 | Carboplatin | Brain |
| Celecoxib | Compound M4 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M4 | Ketoconazole | Prostate |
| Celecoxib | Compound M4 | Cisplatin | |
| Celecoxib | Compound M5 | Anastrozole | Breast |
| Celecoxib | Compound M5 | Capecitabine | Breast |
| Celecoxib | Compound M5 | Docetaxel | Breast, Pancreas |
| Celecoxib | Compound M5 | Gemcitabine | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M5 | Letrozole | Breast |
| Celecoxib | Compound M5 | Megestrol | Breast |
| Celecoxib | Compound M5 | Paclitaxel | Breast |
| Celecoxib | Compound M5 | Tamoxifen | Breast |
| Celecoxib | Compound M5 | Toremifene | Breast, Lung |
| Celecoxib | Compound M5 | Vinorelbine | Lung |
| Celecoxib | Compound M5 | Topotecan | Lung |
| Celecoxib | Compound M5 | Etoposide | Colon |
| Celecoxib | Compound M5 | Fluorouracil | Colon, Bladder |
| Celecoxib | Compound M5 | Irinotecan (CPT-11) | Colon |
| Celecoxib | Compound M5 | Retinoids | Colon |
| Celecoxib | Compound M5 | DFMO | Colon |
| Celecoxib | Compound M5 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M5 | calcium carbonate | Colon |
| Celecoxib | Compound M5 | selenium | Colon |
| Celecoxib | Compound M5 | sulindac sulfone | Colon |
| Celecoxib | Compound M5 | Carboplatin | Brain |
| Celecoxib | Compound M5 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M5 | Ketoconazole | Prostate |
| Celecoxib | Compound M5 | Cisplatin | |
| Celecoxib | Compound M7 | Anastrozole | Breast |
| Celecoxib | Compound M7 | Capecitabine | Breast |
| Celecoxib | Compound M7 | Docetaxel | Breast, Pancreas |

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| | | | |
|-----------|-------------|------------------------|-------------------|
| Celecoxib | Compound M7 | Gemcitabine | Breast |
| Celecoxib | Compound M7 | Letrozole | Breast |
| Celecoxib | Compound M7 | Megestrol | Breast |
| Celecoxib | Compound M7 | Paclitaxel | Breast |
| Celecoxib | Compound M7 | Tamoxifen | Breast |
| Celecoxib | Compound M7 | Toremifene | Breast, Lung |
| Celecoxib | Compound M7 | Vinorelbine | Lung |
| Celecoxib | Compound M7 | Topotecan | Lung |
| Celecoxib | Compound M7 | Etoposide | Colon |
| Celecoxib | Compound M7 | Fluorouracil | Colon, Bladder |
| Celecoxib | Compound M7 | Irinotecan (CPT-11) | Colon |
| Celecoxib | Compound M7 | Retinoids | Colon |
| Celecoxib | Compound M7 | DFMO | Colon |
| Celecoxib | Compound M7 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M7 | calcium carbonate | Colon |
| Celecoxib | Compound M7 | selenium | Colon |
| Celecoxib | Compound M7 | sulindac sulfone | Colon |
| Celecoxib | Compound M7 | Carboplatin | Brain |
| Celecoxib | Compound M7 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M7 | Ketoconazole | Prostate |
| Celecoxib | Compound M7 | Cisplatin | |
| Celecoxib | Bay-12-9566 | Anastrozole | Colon |
| Celecoxib | Bay-12-9566 | Capecitabine | Brain |

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| | | | |
|-----------|-------------|------------------------|-------------------|
| Celecoxib | Bay-12-9566 | Docetaxel | Prostate |
| Celecoxib | Bay-12-9566 | Gemcitabine | Prostate |
| Celecoxib | Bay-12-9566 | Letrozole | Breast |
| Celecoxib | Bay-12-9566 | Megestrol | Breast |
| Celecoxib | Bay-12-9566 | Paclitaxel | Breast |
| Celecoxib | Bay-12-9566 | Tamoxifen | Breast |
| Celecoxib | Bay-12-9566 | Toremifene | Breast |
| Celecoxib | Bay-12-9566 | Vinorelbine | Breast, Lung |
| Celecoxib | Bay-12-9566 | Topotecan | Lung |
| Celecoxib | Bay-12-9566 | Etoposide | Lung |
| Celecoxib | Bay-12-9566 | Fluorouracil | Colon |
| Celecoxib | Bay-12-9566 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Bay-12-9566 | Retinoids | Colon |
| Celecoxib | Bay-12-9566 | DFMO | Colon |
| Celecoxib | Bay-12-9566 | Ursodeoxycholic acid | Colon |
| Celecoxib | Bay-12-9566 | calcium carbonate | Colon |
| Celecoxib | Bay-12-9566 | selenium | Colon |
| Celecoxib | Bay-12-9566 | sulindac sulfone | Colon |
| Celecoxib | Bay-12-9566 | Carboplatin | Brain |
| Celecoxib | Bay-12-9566 | Goserelin Acetate | Prostate |
| Celecoxib | Bay-12-9566 | Ketoconazole | Prostate |
| Celecoxib | Bay-12-9566 | Cisplatin | |
| Celecoxib | Metastat | Anastrozole | Breast |
| Celecoxib | Metastat | Capecitabine | Breast |
| Celecoxib | Metastat | Docetaxel | Breast |

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| | | | |
|-----------|----------|------------------------|---------------------|
| Celecoxib | Metastat | Gemcitabine | Breast, Pancreas |
| Celecoxib | Metastat | Letrozole | Breast |
| Celecoxib | Metastat | Megestrol | Breast |
| Celecoxib | Metastat | Paclitaxel | Breast |
| Celecoxib | Metastat | Tamoxifen | Breast |
| Celecoxib | Metastat | Toremifene | Breast |
| Celecoxib | Metastat | Vinorelbine | Breast, Lung |
| Celecoxib | Metastat | Topotecan | Lung |
| Celecoxib | Metastat | Etoposide | Lung |
| Celecoxib | Metastat | Fluorouracil | Colon |
| Celecoxib | Metastat | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Metastat | Retinoids | Colon |
| Celecoxib | Metastat | DFMO | Colon |
| Celecoxib | Metastat | Ursodeoxycholic acid | Colon |
| Celecoxib | Metastat | calcium carbonate | Colon |
| Celecoxib | Metastat | selenium | Colon |
| Celecoxib | Metastat | sulindac sulfone | Colon |
| Celecoxib | Metastat | Carboplatin | Brain |
| Celecoxib | Metastat | Goserelin Acetate | Prostate |
| Celecoxib | Metastat | Ketoconazole | Prostate |
| Celecoxib | Metastat | Cisplatin | |
| Celecoxib | D-2163 | Anastrozole | Breast |
| Celecoxib | D-2163 | Capecitabine | Breast |
| Celecoxib | D-2163 | Docetaxel | Breast |

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| | | | |
|-----------|--------|------------------------|---------------------|
| Celecoxib | D-2163 | Gemcitabine | Breast, Pancreas |
| Celecoxib | D-2163 | Letrozole | Breast |
| Celecoxib | D-2163 | Megestrol | Breast |
| Celecoxib | D-2163 | Paclitaxel | Breast |
| Celecoxib | D-2163 | Tamoxifen | Breast |
| Celecoxib | D-2163 | Toremifene | Breast |
| Celecoxib | D-2163 | Vinorelbine | Breast, Lung |
| Celecoxib | D-2163 | Topotecan | Lung |
| Celecoxib | D-2163 | Etoposide | Lung |
| Celecoxib | D-2163 | Fluorouracil | Colon |
| Celecoxib | D-2163 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | D-2163 | Retinoids | Colon |
| Celecoxib | D-2163 | DFMO | Colon |
| Celecoxib | D-2163 | Ursodeoxycholic acid | Colon |
| Celecoxib | D-2163 | calcium carbonate | Colon |
| Celecoxib | D-2163 | selenium | Colon |
| Celecoxib | D-2163 | sulindac sulfone | Colon |
| Celecoxib | D-2163 | Carboplatin | Brain |
| Celecoxib | D-2163 | Goserelin Acetate | Prostate |
| Celecoxib | D-2163 | Ketoconazole | Prostate |
| Celecoxib | D-2163 | Cisplatin | |
| Celecoxib | D-1927 | Anastrozole | Breast |
| Celecoxib | D-1927 | Capecitabine | Breast |
| Celecoxib | D-1927 | Docetaxel | Breast |

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| | | | |
|-----------|-------------|--------------------------|---------------------|
| Celecoxib | D-1927 | Gemcitabine | Breast, Pancreas |
| Celecoxib | D-1927 | Letrozole | Breast |
| Celecoxib | D-1927 | Megestrol | Breast |
| Celecoxib | D-1927 | Paclitaxel | Breast |
| Celecoxib | D-1927 | Tamoxifen | Breast |
| Celecoxib | D-1927 | Toremifene | Breast |
| Celecoxib | D-1927 | Vinorelbine | Breast, Lung |
| Celecoxib | D-1927 | Topotecan | Lung |
| Celecoxib | D-1927 | Etoposide | Lung |
| Celecoxib | D-1927 | Fluorouracil | Colon |
| Celecoxib | D-1927 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | D-1927 | Retinoids | Colon |
| Celecoxib | D-1927 | DFMO | Colon |
| Celecoxib | D-1927 | Ursodeoxycholi c acid | Colon |
| Celecoxib | D-1927 | calcium carbonate | Colon |
| Celecoxib | D-1927 | selenium | Colon |
| Celecoxib | D-1927 | sulindac sulfone | Colon |
| Celecoxib | D-1927 | Carboplatin | Brain |
| Celecoxib | D-1927 | Goserelin Acetate | Prostate |
| Celecoxib | D-1927 | Ketoconazole | Prostate |
| Celecoxib | D-1927 | Cisplatin | |
| Celecoxib | Compound M1 | Anastrozole | Breast |
| Celecoxib | Compound M1 | Capecitabine | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M1 | Docetaxel | Breast |
| Celecoxib | Compound M1 | Gemcitabine | Breast, Pancreas |
| Celecoxib | Compound M1 | Letrozole | Breast |
| Celecoxib | Compound M1 | Megestrol | Breast |
| Celecoxib | Compound M1 | Paclitaxel | Breast |
| Celecoxib | Compound M1 | Tamoxifen | Breast |
| Celecoxib | Compound M1 | Toremifene | Breast |
| Celecoxib | Compound M1 | Vinorelbine | Breast, Lung |
| Celecoxib | Compound M1 | Topotecan | Lung |
| Celecoxib | Compound M1 | Etoposide | Lung |
| Celecoxib | Compound M1 | Fluorouracil | Colon |
| Celecoxib | Compound M1 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Compound M1 | Retinoids | Colon |
| Celecoxib | Compound M1 | DFMO | Colon |
| Celecoxib | Compound M1 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M1 | calcium carbonate | Colon |
| Celecoxib | Compound M1 | selenium | Colon |
| Celecoxib | Compound M1 | sulindac sulfone | Colon |
| Celecoxib | Compound M1 | Carboplatin | Brain |
| Celecoxib | Compound M1 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M1 | Ketoconazole | Prostate |
| Celecoxib | Compound M1 | Cisplatin | |
| Celecoxib | Compound M2 | Anastrozole | Breast |
| Celecoxib | Compound M2 | Capecitabine | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M2 | Docetaxel | Breast |
| Celecoxib | Compound M2 | Gemcitabine | Breast, Pancreas |
| Celecoxib | Compound M2 | Letrozole | Breast |
| Celecoxib | Compound M2 | Megestrol | Breast |
| Celecoxib | Compound M2 | Paclitaxel | Breast |
| Celecoxib | Compound M2 | Tamoxifen | Breast |
| Celecoxib | Compound M2 | Toremifene | Breast |
| Celecoxib | Compound M2 | Vinorelbine | Breast, Lung |
| Celecoxib | Compound M2 | Topotecan | Lung |
| Celecoxib | Compound M2 | Etoposide | Lung |
| Celecoxib | Compound M2 | Fluorouracil | Colon |
| Celecoxib | Compound M2 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Compound M2 | Retinoids | Colon |
| Celecoxib | Compound M2 | DFMO | Colon |
| Celecoxib | Compound M2 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M2 | calcium carbonate | Colon |
| Celecoxib | Compound M2 | selenium | Colon |
| Celecoxib | Compound M2 | sulindac sulfone | Colon |
| Celecoxib | Compound M2 | Carboplatin | Brain |
| Celecoxib | Compound M2 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M2 | Ketoconazole | Prostate |
| Celecoxib | Compound M2 | Cisplatin | |
| Celecoxib | Compound M3 | Anastrozole | Breast |
| Celecoxib | Compound M3 | Capecitabine | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M3 | Docetaxel | Breast |
| Celecoxib | Compound M3 | Gemcitabine | Breast, Pancreas |
| Celecoxib | Compound M3 | Letrozole | Breast |
| Celecoxib | Compound M3 | Megestrol | Breast |
| Celecoxib | Compound M3 | Paclitaxel | Breast |
| Celecoxib | Compound M3 | Tamoxifen | Breast |
| Celecoxib | Compound M3 | Toremifene | Breast |
| Celecoxib | Compound M3 | Vinorelbine | Breast, Lung |
| Celecoxib | Compound M3 | Topotecan | Lung |
| Celecoxib | Compound M3 | Etoposide | Lung |
| Celecoxib | Compound M3 | Fluorouracil | Colon |
| Celecoxib | Compound M3 | Irinotecan (CPT-11) | Colon, Bladder |
| Celecoxib | Compound M3 | Retinoids | Colon |
| Celecoxib | Compound M3 | DFMO | Colon |
| Celecoxib | Compound M3 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M3 | calcium carbonate | Colon |
| Celecoxib | Compound M3 | selenium | Colon |
| Celecoxib | Compound M3 | sulindac sulfone | Colon |
| Celecoxib | Compound M3 | Carboplatin | Brain |
| Celecoxib | Compound M3 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M3 | Ketoconazole | Prostate |
| Celecoxib | Compound M3 | Cisplatin | |
| Celecoxib | Compound M4 | Anastrozole | Breast |
| Celecoxib | Compound M4 | Capecitabine | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M4 | Docetaxel | Breast, Pancreas |
| Celecoxib | Compound M4 | Gemcitabine | Breast |
| Celecoxib | Compound M4 | Letrozole | Breast |
| Celecoxib | Compound M4 | Megestrol | Breast |
| Celecoxib | Compound M4 | Paclitaxel | Breast |
| Celecoxib | Compound M4 | Tamoxifen | Breast |
| Celecoxib | Compound M4 | Toremifene | Breast, Lung |
| Celecoxib | Compound M4 | Vinorelbine | Lung |
| Celecoxib | Compound M4 | Topotecan | Lung |
| Celecoxib | Compound M4 | Etoposide | Colon |
| Celecoxib | Compound M4 | Fluorouracil | Colon, Bladder |
| Celecoxib | Compound M4 | Irinotecan (CPT-11) | Colon |
| Celecoxib | Compound M4 | Retinoids | Colon |
| Celecoxib | Compound M4 | DFMO | Colon |
| Celecoxib | Compound M4 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M4 | calcium carbonate | Colon |
| Celecoxib | Compound M4 | selenium | Colon |
| Celecoxib | Compound M4 | sulindac sulfone | Colon |
| Celecoxib | Compound M4 | Carboplatin | Brain |
| Celecoxib | Compound M4 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M4 | Ketoconazole | Prostate |
| Celecoxib | Compound M4 | Cisplatin | |
| Celecoxib | Compound M5 | Anastrozole | Breast |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M5 | Capecitabine | Breast |
| Celecoxib | Compound M5 | Docetaxel | Breast, Pancreas |
| Celecoxib | Compound M5 | Gemcitabine | Breast |
| Celecoxib | Compound M5 | Letrozole | Breast |
| Celecoxib | Compound M5 | Megestrol | Breast |
| Celecoxib | Compound M5 | Paclitaxel | Breast |
| Celecoxib | Compound M5 | Tamoxifen | Breast |
| Celecoxib | Compound M5 | Toremifene | Breast, Lung |
| Celecoxib | Compound M5 | Vinorelbine | Lung |
| Celecoxib | Compound M5 | Topotecan | Lung |
| Celecoxib | Compound M5 | Etoposide | Colon |
| Celecoxib | Compound M5 | Fluorouracil | Colon, Bladder |
| Celecoxib | Compound M5 | Irinotecan (CPT-11) | Colon |
| Celecoxib | Compound M5 | Retinoids | Colon |
| Celecoxib | Compound M5 | DFMO | Colon |
| Celecoxib | Compound M5 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M5 | calcium carbonate | Colon |
| Celecoxib | Compound M5 | selenium | Colon |
| Celecoxib | Compound M5 | sulindac sulfone | Colon |
| Celecoxib | Compound M5 | Carboplatin | Brain |
| Celecoxib | Compound M5 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M5 | Ketoconazole | Prostate |
| Celecoxib | Compound M5 | Cisplatin | |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Celecoxib | Compound M7 | Anastrozole | Breast |
| Celecoxib | Compound M7 | Capecitabine | Breast |
| Celecoxib | Compound M7 | Docetaxel | Breast, Pancreas |
| Celecoxib | Compound M7 | Gemcitabine | Breast |
| Celecoxib | Compound M7 | Letrozole | Breast |
| Celecoxib | Compound M7 | Megestrol | Breast |
| Celecoxib | Compound M7 | Paclitaxel | Breast |
| Celecoxib | Compound M7 | Tamoxifen | Breast |
| Celecoxib | Compound M7 | Toremifene | Breast, Lung |
| Celecoxib | Compound M7 | Vinorelbine | Lung |
| Celecoxib | Compound M7 | Topotecan | Lung |
| Celecoxib | Compound M7 | Etoposide | Colon |
| Celecoxib | Compound M7 | Fluorouracil | Colon, Bladder |
| Celecoxib | Compound M7 | Irinotecan (CPT-11) | Colon |
| Celecoxib | Compound M7 | Retinoids | Colon |
| Celecoxib | Compound M7 | DFMO | Colon |
| Celecoxib | Compound M7 | Ursodeoxycholic acid | Colon |
| Celecoxib | Compound M7 | calcium carbonate | Colon |
| Celecoxib | Compound M7 | selenium | Colon |
| Celecoxib | Compound M7 | sulindac sulfone | Colon |
| Celecoxib | Compound M7 | Carboplatin | Brain |
| Celecoxib | Compound M7 | Goserelin Acetate | Prostate |
| Celecoxib | Compound M7 | Ketoconazole | Prostate |

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| | | | |
|-----------|-------------|--------------------------|-------------------|
| Celecoxib | Compound M7 | Cisplatin | |
| Rofecoxib | Bay-12-9566 | Anastrozole | Colon |
| Rofecoxib | Bay-12-9566 | Capecitabine | Brain |
| Rofecoxib | Bay-12-9566 | Docetaxel | Prostate |
| Rofecoxib | Bay-12-9566 | Gemcitabine | Prostate |
| Rofecoxib | Bay-12-9566 | Letrozole | Breast |
| Rofecoxib | Bay-12-9566 | Megestrol | Breast |
| Rofecoxib | Bay-12-9566 | Paclitaxel | Breast |
| Rofecoxib | Bay-12-9566 | Tamoxifen | Breast |
| Rofecoxib | Bay-12-9566 | Toremifene | Breast |
| Rofecoxib | Bay-12-9566 | Vinorelbine | Breast, Lung |
| Rofecoxib | Bay-12-9566 | Topotecan | Lung |
| Rofecoxib | Bay-12-9566 | Etoposide | Lung |
| Rofecoxib | Bay-12-9566 | Fluorouracil | Colon |
| Rofecoxib | Bay-12-9566 | Irinotecan (CPT-11) | Colon, Bladder |
| Rofecoxib | Bay-12-9566 | Retinoids | Colon |
| Rofecoxib | Bay-12-9566 | DFMO | Colon |
| Rofecoxib | Bay-12-9566 | Ursodeoxycholi c acid | Colon |
| Rofecoxib | Bay-12-9566 | calcium carbonate | Colon |
| Rofecoxib | Bay-12-9566 | selenium | Colon |
| Rofecoxib | Bay-12-9566 | sulindac sulfone | Colon |
| Rofecoxib | Bay-12-9566 | Carboplatin | Brain |
| Rofecoxib | Bay-12-9566 | Goserelin Acetate | Prostate |
| Rofecoxib | Bay-12-9566 | Ketoconazole | Prostate |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Rofecoxib | Bay-12-9566 | Cisplatin | |
| Rofecoxib | Metastat | Anastrozole | Breast |
| Rofecoxib | Metastat | Capecitabine | Breast |
| Rofecoxib | Metastat | Docetaxel | Breast |
| Rofecoxib | Metastat | Gemcitabine | Breast, Pancreas |
| Rofecoxib | Metastat | Letrozole | Breast |
| Rofecoxib | Metastat | Megestrol | Breast |
| Rofecoxib | Metastat | Paclitaxel | Breast |
| Rofecoxib | Metastat | Tamoxifen | Breast |
| Rofecoxib | Metastat | Toremifene | Breast |
| Rofecoxib | Metastat | Vinorelbine | Breast, Lung |
| Rofecoxib | Metastat | Topotecan | Lung |
| Rofecoxib | Metastat | Etoposide | Lung |
| Rofecoxib | Metastat | Fluorouracil | Colon |
| Rofecoxib | Metastat | Irinotecan (CPT-11) | Colon, Bladder |
| Rofecoxib | Metastat | Retinoids | Colon |
| Rofecoxib | Metastat | DFMO | Colon |
| Rofecoxib | Metastat | Ursodeoxycholic acid | Colon |
| Rofecoxib | Metastat | calcium carbonate | Colon |
| Rofecoxib | Metastat | selenium | Colon |
| Rofecoxib | Metastat | sulindac sulfone | Colon |
| Rofecoxib | Metastat | Carboplatin | Brain |
| Rofecoxib | Metastat | Goserelin Acetate | Prostate |
| Rofecoxib | Metastat | Ketoconazole | Prostate |

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| | | | |
|-----------|----------|------------------------|---------------------|
| Rofecoxib | Metastat | Cisplatin | |
| Rofecoxib | D-2163 | Anastrozole | Breast |
| Rofecoxib | D-2163 | Capecitabine | Breast |
| Rofecoxib | D-2163 | Docetaxel | Breast |
| Rofecoxib | D-2163 | Gemcitabine | Breast, Pancreas |
| Rofecoxib | D-2163 | Letrozole | Breast |
| Rofecoxib | D-2163 | Megestrol | Breast |
| Rofecoxib | D-2163 | Paclitaxel | Breast |
| Rofecoxib | D-2163 | Tamoxifen | Breast |
| Rofecoxib | D-2163 | Toremifene | Breast |
| Rofecoxib | D-2163 | Vinorelbine | Breast, Lung |
| Rofecoxib | D-2163 | Topotecan | Lung |
| Rofecoxib | D-2163 | Etoposide | Lung |
| Rofecoxib | D-2163 | Fluorouracil | Colon |
| Rofecoxib | D-2163 | Irinotecan (CPT-11) | Colon, Bladder |
| Rofecoxib | D-2163 | Retinoids | Colon |
| Rofecoxib | D-2163 | DFMO | Colon |
| Rofecoxib | D-2163 | Ursodeoxycholic acid | Colon |
| Rofecoxib | D-2163 | calcium carbonate | Colon |
| Rofecoxib | D-2163 | selenium | Colon |
| Rofecoxib | D-2163 | sulindac sulfone | Colon |
| Rofecoxib | D-2163 | Carboplatin | Brain |
| Rofecoxib | D-2163 | Goserelin Acetate | Prostate |
| Rofecoxib | D-2163 | Ketoconazole | Prostate |

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| | | | |
|-----------|--------|------------------------|---------------------|
| Rofecoxib | D-2163 | Cisplatin | |
| Rofecoxib | D-1927 | Anastrozole | Breast |
| Rofecoxib | D-1927 | Capecitabine | Breast |
| Rofecoxib | D-1927 | Docetaxel | Breast |
| Rofecoxib | D-1927 | Gemcitabine | Breast, Pancreas |
| Rofecoxib | D-1927 | Letrozole | Breast |
| Rofecoxib | D-1927 | Megestrol | Breast |
| Rofecoxib | D-1927 | Paclitaxel | Breast |
| Rofecoxib | D-1927 | Tamoxifen | Breast |
| Rofecoxib | D-1927 | Toremifene | Breast |
| Rofecoxib | D-1927 | Vinorelbine | Breast, Lung |
| Rofecoxib | D-1927 | Topotecan | Lung |
| Rofecoxib | D-1927 | Etoposide | Lung |
| Rofecoxib | D-1927 | Fluorouracil | Colon |
| Rofecoxib | D-1927 | Irinotecan (CPT-11) | Colon, Bladder |
| Rofecoxib | D-1927 | Retinoids | Colon |
| Rofecoxib | D-1927 | DFMO | Colon |
| Rofecoxib | D-1927 | Ursodeoxycholic acid | Colon |
| Rofecoxib | D-1927 | calcium carbonate | Colon |
| Rofecoxib | D-1927 | selenium | Colon |
| Rofecoxib | D-1927 | sulindac sulfone | Colon |
| Rofecoxib | D-1927 | Carboplatin | Brain |
| Rofecoxib | D-1927 | Goserelin Acetate | Prostate |
| Rofecoxib | D-1927 | Ketoconazole | Prostate |

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| | | | |
|-----------|-------------|------------------------|---------------------|
| Rofecoxib | D-1927 | Cisplatin | |
| JTE-522 | Compound M1 | Anastrozole | Breast |
| JTE-522 | Compound M1 | Capecitabine | Breast |
| JTE-522 | Compound M1 | Docetaxel | Breast |
| JTE-522 | Compound M1 | Gemcitabine | Breast, Pancreas |
| JTE-522 | Compound M1 | Letrozole | Breast |
| JTE-522 | Compound M1 | Megestrol | Breast |
| JTE-522 | Compound M1 | Paclitaxel | Breast |
| JTE-522 | Compound M1 | Tamoxifen | Breast |
| JTE-522 | Compound M1 | Toremifene | Breast |
| JTE-522 | Compound M1 | Vinorelbine | Breast, Lung |
| JTE-522 | Compound M1 | Topotecan | Lung |
| JTE-522 | Compound M1 | Etoposide | Lung |
| JTE-522 | Compound M1 | Fluorouracil | Colon |
| JTE-522 | Compound M1 | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | Compound M1 | Retinoids | Colon |
| JTE-522 | Compound M1 | DFMO | Colon |
| JTE-522 | Compound M1 | Ursodeoxycholic acid | Colon |
| JTE-522 | Compound M1 | calcium carbonate | Colon |
| JTE-522 | Compound M1 | selenium | Colon |
| JTE-522 | Compound M1 | sulindac sulfone | Colon |
| JTE-522 | Compound M1 | Carboplatin | Brain |
| JTE-522 | Compound M1 | Goserelin Acetate | Prostate |

| | | | |
|---------|-------------|------------------------|---------------------|
| JTE-522 | Compound M1 | Ketoconazole | Prostate |
| JTE-522 | Compound M1 | Cisplatin | |
| JTE-522 | Compound M2 | Anastrozole | Breast |
| JTE-522 | Compound M2 | Capecitabine | Breast |
| JTE-522 | Compound M2 | Docetaxel | Breast |
| JTE-522 | Compound M2 | Gemcitabine | Breast, Pancreas |
| JTE-522 | Compound M2 | Letrozole | Breast |
| JTE-522 | Compound M2 | Megestrol | Breast |
| JTE-522 | Compound M2 | Paclitaxel | Breast |
| JTE-522 | Compound M2 | Tamoxifen | Breast |
| JTE-522 | Compound M2 | Toremifene | Breast |
| JTE-522 | Compound M2 | Vinorelbine | Breast, Lung |
| JTE-522 | Compound M2 | Topotecan | Lung |
| JTE-522 | Compound M2 | Etoposide | Lung |
| JTE-522 | Compound M2 | Fluorouracil | Colon |
| JTE-522 | Compound M2 | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | Compound M2 | Retinoids | Colon |
| JTE-522 | Compound M2 | DFMO | Colon |
| JTE-522 | Compound M2 | Ursodeoxycholic acid | Colon |
| JTE-522 | Compound M2 | calcium carbonate | Colon |
| JTE-522 | Compound M2 | selenium | Colon |
| JTE-522 | Compound M2 | sulindac sulfone | Colon |
| JTE-522 | Compound M2 | Carboplatin | Brain |
| JTE-522 | Compound M2 | Goserelin Acetate | Prostate |

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| | | | |
|---------|-------------|------------------------|---------------------|
| JTE-522 | Compound M2 | Ketoconazole | Prostate |
| JTE-522 | Compound M2 | Cisplatin | |
| JTE-522 | Compound M3 | Anastrozole | Breast |
| JTE-522 | Compound M3 | Capecitabine | Breast |
| JTE-522 | Compound M3 | Docetaxel | Breast |
| JTE-522 | Compound M3 | Gemcitabine | Breast, Pancreas |
| JTE-522 | Compound M3 | Letrozole | Breast |
| JTE-522 | Compound M3 | Megestrol | Breast |
| JTE-522 | Compound M3 | Paclitaxel | Breast |
| JTE-522 | Compound M3 | Tamoxifen | Breast |
| JTE-522 | Compound M3 | Toremifene | Breast |
| JTE-522 | Compound M3 | Vinorelbine | Breast, Lung |
| JTE-522 | Compound M3 | Topotecan | Lung |
| JTE-522 | Compound M3 | Etoposide | Lung |
| JTE-522 | Compound M3 | Fluorouracil | Colon |
| JTE-522 | Compound M3 | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | Compound M3 | Retinoids | Colon |
| JTE-522 | Compound M3 | DFMO | Colon |
| JTE-522 | Compound M3 | Ursodeoxycholic acid | Colon |
| JTE-522 | Compound M3 | calcium carbonate | Colon |
| JTE-522 | Compound M3 | selenium | Colon |
| JTE-522 | Compound M3 | sulindac sulfone | Colon |
| JTE-522 | Compound M3 | Carboplatin | Brain |
| JTE-522 | Compound M3 | Goserelin Acetate | Prostate |

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| | | | |
|---------|-------------|------------------------|---------------------|
| JTE-522 | Compound M3 | Ketoconazole | Prostate |
| JTE-522 | Compound M3 | Cisplatin | |
| JTE-522 | Compound M4 | Anastrozole | Breast |
| JTE-522 | Compound M4 | Capecitabine | Breast |
| JTE-522 | Compound M4 | Docetaxel | Breast, Pancreas |
| JTE-522 | Compound M4 | Gemcitabine | Breast |
| JTE-522 | Compound M4 | Letrozole | Breast |
| JTE-522 | Compound M4 | Megestrol | Breast |
| JTE-522 | Compound M4 | Paclitaxel | Breast |
| JTE-522 | Compound M4 | Tamoxifen | Breast |
| JTE-522 | Compound M4 | Toremifene | Breast, Lung |
| JTE-522 | Compound M4 | Vinorelbine | Lung |
| JTE-522 | Compound M4 | Topotecan | Lung |
| JTE-522 | Compound M4 | Etoposide | Colon |
| JTE-522 | Compound M4 | Fluorouracil | Colon, Bladder |
| JTE-522 | Compound M4 | Irinotecan (CPT-11) | Colon |
| JTE-522 | Compound M4 | Retinoids | Colon |
| JTE-522 | Compound M4 | DFMO | Colon |
| JTE-522 | Compound M4 | Ursodeoxycholic acid | Colon |
| JTE-522 | Compound M4 | calcium carbonate | Colon |
| JTE-522 | Compound M4 | selenium | Colon |
| JTE-522 | Compound M4 | sulindac sulfone | Colon |
| JTE-522 | Compound M4 | Carboplatin | Brain |
| JTE-522 | Compound M4 | Goserelin | Prostate |

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| Acetate | | | |
|---------|-------------|------------------------|---------------------|
| JTE-522 | Compound M4 | Ketoconazole | Prostate |
| JTE-522 | Compound M4 | Cisplatin | |
| JTE-522 | Compound M5 | Anastrozole | Breast |
| JTE-522 | Compound M5 | Capecitabine | Breast |
| JTE-522 | Compound M5 | Docetaxel | Breast, Pancreas |
| JTE-522 | Compound M5 | Gemcitabine | Breast |
| JTE-522 | Compound M5 | Letrozole | Breast |
| JTE-522 | Compound M5 | Megestrol | Breast |
| JTE-522 | Compound M5 | Paclitaxel | Breast |
| JTE-522 | Compound M5 | Tamoxifen | Breast |
| JTE-522 | Compound M5 | Toremifene | Breast, Lung |
| JTE-522 | Compound M5 | Vinorelbine | Lung |
| JTE-522 | Compound M5 | Topotecan | Lung |
| JTE-522 | Compound M5 | Etoposide | Colon |
| JTE-522 | Compound M5 | Fluorouracil | Colon, Bladder |
| JTE-522 | Compound M5 | Irinotecan (CPT-11) | Colon |
| JTE-522 | Compound M5 | Retinoids | Colon |
| JTE-522 | Compound M5 | DFMO | Colon |
| JTE-522 | Compound M5 | Ursodeoxycholic acid | Colon |
| JTE-522 | Compound M5 | calcium carbonate | Colon |
| JTE-522 | Compound M5 | selenium | Colon |
| JTE-522 | Compound M5 | sulindac sulfone | Colon |
| JTE-522 | Compound M5 | Carboplatin | Brain |

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| | | | |
|---------|-------------|--------------------------|---------------------|
| JTE-522 | Compound M5 | Goserelin Acetate | Prostate |
| JTE-522 | Compound M5 | Ketoconazole | Prostate |
| JTE-522 | Compound M5 | Cisplatin | |
| JTE-522 | Compound M7 | Anastrozole | Breast |
| JTE-522 | Compound M7 | Capecitabine | Breast |
| JTE-522 | Compound M7 | Docetaxel | Breast, Pancreas |
| JTE-522 | Compound M7 | Gemcitabine | Breast |
| JTE-522 | Compound M7 | Letrozole | Breast |
| JTE-522 | Compound M7 | Megestrol | Breast |
| JTE-522 | Compound M7 | Paclitaxel | Breast |
| JTE-522 | Compound M7 | Tamoxifen | Breast |
| JTE-522 | Compound M7 | Toremifene | Breast, Lung |
| JTE-522 | Compound M7 | Vinorelbine | Lung |
| JTE-522 | Compound M7 | Topotecan | Lung |
| JTE-522 | Compound M7 | Etoposide | Colon |
| JTE-522 | Compound M7 | Fluorouracil | Colon, Bladder |
| JTE-522 | Compound M7 | Irinotecan (CPT-11) | Colon |
| JTE-522 | Compound M7 | Retinoids | Colon |
| JTE-522 | Compound M7 | DFMO | Colon |
| JTE-522 | Compound M7 | Ursodeoxycholi c acid | Colon |
| JTE-522 | Compound M7 | calcium carbonate | Colon |
| JTE-522 | Compound M7 | selenium | Colon |
| JTE-522 | Compound M7 | sulindac sulfone | Colon |

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| | | | |
|---------|-------------|--------------------------|-------------------|
| JTE-522 | Compound M7 | Carboplatin | Brain |
| JTE-522 | Compound M7 | Goserelin Acetate | Prostate |
| JTE-522 | Compound M7 | Ketoconazole | Prostate |
| JTE-522 | Compound M7 | Cisplatin | |
| JTE-522 | Bay-12-9566 | Anastrozole | Colon |
| JTE-522 | Bay-12-9566 | Capecitabine | Brain |
| JTE-522 | Bay-12-9566 | Docetaxel | Prostate |
| JTE-522 | Bay-12-9566 | Gemcitabine | Prostate |
| JTE-522 | Bay-12-9566 | Letrozole | Breast |
| JTE-522 | Bay-12-9566 | Megestrol | Breast |
| JTE-522 | Bay-12-9566 | Paclitaxel | Breast |
| JTE-522 | Bay-12-9566 | Tamoxifen | Breast |
| JTE-522 | Bay-12-9566 | Toremifene | Breast |
| JTE-522 | Bay-12-9566 | Vinorelbine | Breast, Lung |
| JTE-522 | Bay-12-9566 | Topotecan | Lung |
| JTE-522 | Bay-12-9566 | Etoposide | Lung |
| JTE-522 | Bay-12-9566 | Fluorouracil | Colon |
| JTE-522 | Bay-12-9566 | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | Bay-12-9566 | Retinoids | Colon |
| JTE-522 | Bay-12-9566 | DFMO | Colon |
| JTE-522 | Bay-12-9566 | Ursodeoxycholi c acid | Colon |
| JTE-522 | Bay-12-9566 | calcium carbonate | Colon |
| JTE-522 | Bay-12-9566 | selenium | Colon |
| JTE-522 | Bay-12-9566 | sulindac sulfone | Colon |

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| | | | |
|---------|-------------|--------------------------|---------------------|
| JTE-522 | Bay-12-9566 | Carboplatin | Brain |
| JTE-522 | Bay-12-9566 | Goserelin Acetate | Prostate |
| JTE-522 | Bay-12-9566 | Ketoconazole | Prostate |
| JTE-522 | Bay-12-9566 | Cisplatin | |
| JTE-522 | Metastat | Anastrozole | Breast |
| JTE-522 | Metastat | Capecitabine | Breast |
| JTE-522 | Metastat | Docetaxel | Breast |
| JTE-522 | Metastat | Gemcitabine | Breast, Pancreas |
| JTE-522 | Metastat | Letrozole | Breast |
| JTE-522 | Metastat | Megestrol | Breast |
| JTE-522 | Metastat | Paclitaxel | Breast |
| JTE-522 | Metastat | Tamoxifen | Breast |
| JTE-522 | Metastat | Toremifene | Breast |
| JTE-522 | Metastat | Vinorelbine | Breast, Lung |
| JTE-522 | Metastat | Topotecan | Lung |
| JTE-522 | Metastat | Etoposide | Lung |
| JTE-522 | Metastat | Fluorouracil | Colon |
| JTE-522 | Metastat | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | Metastat | Retinoids | Colon |
| JTE-522 | Metastat | DFMO | Colon |
| JTE-522 | Metastat | Ursodeoxycholi c acid | Colon |
| JTE-522 | Metastat | calcium carbonate | Colon |
| JTE-522 | Metastat | selenium | Colon |
| JTE-522 | Metastat | sulindac sulfone | Colon |

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| | | | |
|---------|----------|--------------------------|---------------------|
| JTE-522 | Metastat | Carboplatin | Brain |
| JTE-522 | Metastat | Goserelin Acetate | Prostate |
| JTE-522 | Metastat | Ketoconazole | Prostate |
| JTE-522 | Metastat | Cisplatin | |
| JTE-522 | D-2163 | Anastrozole | Breast |
| JTE-522 | D-2163 | Capecitabine | Breast |
| JTE-522 | D-2163 | Docetaxel | Breast |
| JTE-522 | D-2163 | Gemcitabine | Breast, Pancreas |
| JTE-522 | D-2163 | Letrozole | Breast |
| JTE-522 | D-2163 | Megestrol | Breast |
| JTE-522 | D-2163 | Paclitaxel | Breast |
| JTE-522 | D-2163 | Tamoxifen | Breast |
| JTE-522 | D-2163 | Toremifene | Breast |
| JTE-522 | D-2163 | Vinorelbine | Breast, Lung |
| JTE-522 | D-2163 | Topotecan | Lung |
| JTE-522 | D-2163 | Etoposide | Lung |
| JTE-522 | D-2163 | Fluorouracil | Colon |
| JTE-522 | D-2163 | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | D-2163 | Retinoids | Colon |
| JTE-522 | D-2163 | DFMO | Colon |
| JTE-522 | D-2163 | Ursodeoxycholi c acid | Colon |
| JTE-522 | D-2163 | calcium carbonate | Colon |
| JTE-522 | D-2163 | selenium | Colon |
| JTE-522 | D-2163 | sulindac sulfone | Colon |

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| | | | |
|---------|--------|------------------------|---------------------|
| JTE-522 | D-2163 | Carboplatin | Brain |
| JTE-522 | D-2163 | Goserelin Acetate | Prostate |
| JTE-522 | D-2163 | Ketoconazole | Prostate |
| JTE-522 | D-2163 | Cisplatin | |
| JTE-522 | D-1927 | Anastrozole | Breast |
| JTE-522 | D-1927 | Capecitabine | Breast |
| JTE-522 | D-1927 | Docetaxel | Breast |
| JTE-522 | D-1927 | Gemcitabine | Breast, Pancreas |
| JTE-522 | D-1927 | Letrozole | Breast |
| JTE-522 | D-1927 | Megestrol | Breast |
| JTE-522 | D-1927 | Paclitaxel | Breast |
| JTE-522 | D-1927 | Tamoxifen | Breast |
| JTE-522 | D-1927 | Toremifene | Breast |
| JTE-522 | D-1927 | Vinorelbine | Breast, Lung |
| JTE-522 | D-1927 | Topotecan | Lung |
| JTE-522 | D-1927 | Etoposide | Lung |
| JTE-522 | D-1927 | Fluorouracil | Colon |
| JTE-522 | D-1927 | Irinotecan (CPT-11) | Colon, Bladder |
| JTE-522 | D-1927 | Retinoids | Colon |
| JTE-522 | D-1927 | DFMO | Colon |
| JTE-522 | D-1927 | Ursodeoxycholic acid | Colon |
| JTE-522 | D-1927 | calcium carbonate | Colon |
| JTE-522 | D-1927 | selenium | Colon |
| JTE-522 | D-1927 | sulindac sulfone | Colon |

| | | | |
|---------|--------|----------------------|----------|
| JTE-522 | D-1927 | Carboplatin | Brain |
| JTE-522 | D-1927 | Goserelin Acetate | Prostate |
| JTE-522 | D-1927 | Ketoconazole | Prostate |
| JTE-522 | D-1927 | Cisplatin | |

Further examples of combinations are listed in Table No 24, below.

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Table No. 24.. Further examples of combination therapies

| COX-2 Inhibitor | MMP Inhibitor | Antineoplastic Agent | Indication |
|----------------------------|--------------------------|--|-------------------|
| Celecoxib | Compound M1 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Compound M1 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | Compound M1 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Compound M1 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Celecoxib | Compound M1 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Compound M1 | Cyclophosphamide, Methotrexate, | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Fluorouracil | |
| Celecoxib | Compound M1 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M1 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Compound M1 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Compound M1 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Compound M1 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Compound M1 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | Compound M1 | Etoposide, Carboplatin | Lung |
| Celecoxib | Compound M1 | Etoposide, Cisplatin | Lung |
| Celecoxib | Compound M1 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Compound M1 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Compound M1 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Compound M2 | Doxorubicin and Cyclophosphamide | Breast |

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| | | | |
|-----------|-------------|--|--------|
| Celecoxib | Compound M2 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | Compound M2 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Compound M2 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Celecoxib | Compound M2 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Compound M2 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M2 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M2 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Compound M2 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Compound M2 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Compound M2 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |

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| | | | |
|-----------|-------------|--|--------|
| Celecoxib | Compound M2 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | Compound M2 | Etoposide, Carboplatin | Lung |
| Celecoxib | Compound M2 | Etoposide, Cisplatin | Lung |
| Celecoxib | Compound M2 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Compound M2 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Compound M2 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Compound M3 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Compound M3 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | Compound M3 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Compound M3 | Mitoxantrone, Fluorouracil and Leucovorin | Breast |
| Celecoxib | Compound M3 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Compound M3 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |

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| | | | |
|-----------|-------------|--|--------|
| Celecoxib | Compound M3 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M3 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Compound M3 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Compound M3 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Compound M3 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Compound M3 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | Compound M3 | Etoposide, Carboplatin | Lung |
| Celecoxib | Compound M3 | Etoposide, Cisplatin | Lung |
| Celecoxib | Compound M3 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Compound M3 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Compound M3 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Compound M4 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Compound M4 | Cyclophosphamide, | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Doxorubicin, and Fluorouracil | |
| Celecoxib | Compound M4 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Compound M4 | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| Celecoxib | Compound M4 | Vinblastine,Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Compound M4 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M4 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M4 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Compound M4 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Compound M4 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Compound M4 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Compound M4 | Cyclophosphamide, | Lung |

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| | | | |
|-----------|-------------|--|--------|
| | | Doxorubicin, Vincristine | |
| Celecoxib | Compound M4 | Etoposide, Carboplatin | Lung |
| Celecoxib | Compound M4 | Etoposide, Cisplatin | Lung |
| Celecoxib | Compound M4 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Compound M4 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Compound M4 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Compound M5 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Compound M5 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | Compound M5 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Compound M5 | Mitoxantrone, Fluorouracil and Leucovorin | Breast |
| Celecoxib | Compound M5 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Compound M5 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M5 | Doxorubicin, | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Cyclophosphamide, Methotrexate, Fluorouracil | |
| Celecoxib | Compound M5 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Compound M5 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Compound M5 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Compound M5 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Compound M5 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | Compound M5 | Etoposide, Carboplatin | Lung |
| Celecoxib | Compound M5 | Etoposide, Cisplatin | Lung |
| Celecoxib | Compound M5 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Compound M5 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Compound M5 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Compound M7 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Compound M7 | Cyclophosphamide, Doxorubicin, and | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Fluorouracil | |
| Celecoxib | Compound M7 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Compound M7 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Celecoxib | Compound M7 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Compound M7 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M7 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Compound M7 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Compound M7 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Compound M7 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Compound M7 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Compound M7 | Cyclophosphamide, Doxorubicin, | Lung |

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| | | | |
|-----------|-------------|--|--------|
| | | Vincristine | |
| Celecoxib | Compound M7 | Etoposide, Carboplatin | Lung |
| Celecoxib | Compound M7 | Etoposide, Cisplatin | Lung |
| Celecoxib | Compound M7 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Compound M7 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Compound M7 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Bay-12-9566 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Bay-12-9566 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | Bay-12-9566 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Bay-12-9566 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Celecoxib | Bay-12-9566 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Bay-12-9566 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Bay-12-9566 | Doxorubicin, Cyclophosphamide, | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Methotrexate, Fluorouracil | |
| Celecoxib | Bay-12-9566 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Bay-12-9566 | Fluorouracil, Levamisole | Colon |
| Celecoxib | Bay-12-9566 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Bay-12-9566 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Bay-12-9566 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | Bay-12-9566 | Etoposide, Carboplatin | Lung |
| Celecoxib | Bay-12-9566 | Etoposide, Cisplatin | Lung |
| Celecoxib | Bay-12-9566 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Bay-12-9566 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Bay-12-9566 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | Metastat | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | Metastat | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |

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| | | | |
|-----------|----------|--|--------|
| Celecoxib | Metastat | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | Metastat | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| Celecoxib | Metastat | Vinblastine,Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | Metastat | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Metastat | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | Metastat | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | Metastat | Fluorouracil, Levamisole | Colon |
| Celecoxib | Metastat | Leucovorin, Fluorouracil | Colon |
| Celecoxib | Metastat | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | Metastat | Cyclophosphamide, Doxorubicin, Vincristine | Lung |

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| | | | |
|-----------|----------|--|--------|
| Celecoxib | Metastat | Etoposide, Carboplatin | Lung |
| Celecoxib | Metastat | Etoposide, Cisplatin | Lung |
| Celecoxib | Metastat | Paclitaxel, Carboplatin | Lung |
| Celecoxib | Metastat | Gemcitabine, Cisplatin | Lung |
| Celecoxib | Metastat | Paclitaxel, Cisplatin | Lung |
| Celecoxib | D-2163 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | D-2163 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | D-2163 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Celecoxib | D-2163 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Celecoxib | D-2163 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | D-2163 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | D-2163 | Doxorubicin, Cyclophosphamide, Methotrexate, | Breast |

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| | | | |
|-----------|--------|--|--------|
| | | Fluorouracil | |
| Celecoxib | D-2163 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | D-2163 | Fluorouracil, Levamisole | Colon |
| Celecoxib | D-2163 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | D-2163 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | D-2163 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | D-2163 | Etoposide, Carboplatin | Lung |
| Celecoxib | D-2163 | Etoposide, Cisplatin | Lung |
| Celecoxib | D-2163 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | D-2163 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | D-2163 | Paclitaxel, Cisplatin | Lung |
| Celecoxib | D-1927 | Doxorubicin and Cyclophosphamide | Breast |
| Celecoxib | D-1927 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Celecoxib | D-1927 | Cyclophosphamide, | Breast |

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| | | | |
|-----------|--------|--|--------|
| | | Fluorouracil and Mitoxantrone | |
| Celecoxib | D-1927 | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| Celecoxib | D-1927 | Vinblastine,Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Celecoxib | D-1927 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | D-1927 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Celecoxib | D-1927 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Celecoxib | D-1927 | Fluorouracil, Levamisole | Colon |
| Celecoxib | D-1927 | Leucovorin, Fluorouracil | Colon |
| Celecoxib | D-1927 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Celecoxib | D-1927 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Celecoxib | D-1927 | Etoposide, | Lung |

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| | | | |
|-----------|-------------|--|--------|
| | | Carboplatin | |
| Celecoxib | D-1927 | Etoposide, Cisplatin | Lung |
| Celecoxib | D-1927 | Paclitaxel, Carboplatin | Lung |
| Celecoxib | D-1927 | Gemcitabine, Cisplatin | Lung |
| Celecoxib | D-1927 | Paclitaxel, Cisplatin | Lung |
| | | | |
| Rofecoxib | Compound M1 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Compound M1 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Compound M1 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | Compound M1 | Mitoxantrone, Fluorouracil and Leucovorin | Breast |
| Rofecoxib | Compound M1 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | Compound M1 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M1 | Doxorubicin, Cyclophosphamide, Methotrexate, | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Fluorouracil | |
| Rofecoxib | Compound M1 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | Compound M1 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Compound M1 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Compound M1 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Compound M1 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Compound M1 | Etoposide, Carboplatin | Lung |
| Rofecoxib | Compound M1 | Etoposide, Cisplatin | Lung |
| Rofecoxib | Compound M1 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Compound M1 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Compound M1 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Compound M2 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Compound M2 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Compound M2 | Cyclophosphamide, | Breast |

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| | | | |
|-----------|-------------|--|--------|
| | | Fluorouracil and Mitoxantrone | |
| Rofecoxib | Compound M2 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Rofecoxib | Compound M2 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | Compound M2 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M2 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M2 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | Compound M2 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Compound M2 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Compound M2 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Compound M2 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Compound M2 | Etoposide, | Lung |

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| | | | |
|-----------|-------------|--|--------|
| | | Carboplatin | |
| Rofecoxib | Compound M2 | Etoposide, Cisplatin | Lung |
| Rofecoxib | Compound M2 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Compound M2 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Compound M2 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Compound M3 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Compound M3 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Compound M3 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | Compound M3 | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| Rofecoxib | Compound M3 | Vinblastine,Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | Compound M3 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M3 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |

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| | | | |
|-----------|-------------|--|--------|
| Rofecoxib | Compound M3 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | Compound M3 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Compound M3 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Compound M3 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Compound M3 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Compound M3 | Etoposide, Carboplatin | Lung |
| Rofecoxib | Compound M3 | Etoposide, Cisplatin | Lung |
| Rofecoxib | Compound M3 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Compound M3 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Compound M3 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Compound M4 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Compound M4 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Compound M4 | Cyclophosphamide, Fluorouracil and | Breast |

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| | | | |
|-----------|-------------|---|--------|
| | | Mitoxantrone | |
| Rofecoxib | Compound M4 | Mitoxantrone, Fluorouracil and Leucovorin | Breast |
| Rofecoxib | Compound M4 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | Compound M4 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M4 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M4 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | Compound M4 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Compound M4 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Compound M4 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Compound M4 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Compound M4 | Etoposide, Carboplatin | Lung |

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| | | | |
|-----------|-------------|--|--------|
| Rofecoxib | Compound M4 | Etoposide, Cisplatin | Lung |
| Rofecoxib | Compound M4 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Compound M4 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Compound M4 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Compound M5 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Compound M5 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Compound M5 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | Compound M5 | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| Rofecoxib | Compound M5 | Vinblastine,Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | Compound M5 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M5 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M5 | Vinblastine, | Breast |

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| | | | |
|-----------|-------------|---|--------|
| | | Doxorubicin, Thiotepa, Fluoxymesterone | |
| Rofecoxib | Compound M5 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Compound M5 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Compound M5 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Compound M5 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Compound M5 | Etoposide, Carboplatin | Lung |
| Rofecoxib | Compound M5 | Etoposide, Cisplatin | Lung |
| Rofecoxib | Compound M5 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Compound M5 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Compound M5 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Compound M7 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Compound M7 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Compound M7 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |

| | | | |
|-----------|-------------|--|--------|
| Rofecoxib | Compound M7 | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| Rofecoxib | Compound M7 | Vinblastine,Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | Compound M7 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M7 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Compound M7 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | Compound M7 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Compound M7 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Compound M7 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Compound M7 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Compound M7 | Etoposide, Carboplatin | Lung |
| Rofecoxib | Compound M7 | Etoposide, | Lung |

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| | | | |
|-----------|-------------|--|--------|
| | | Cisplatin | |
| Rofecoxib | Compound M7 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Compound M7 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Compound M7 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Bay-12-9566 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Bay-12-9566 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Bay-12-9566 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | Bay-12-9566 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Rofecoxib | Bay-12-9566 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestron | Breast |
| Rofecoxib | Bay-12-9566 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Bay-12-9566 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Bay-12-9566 | Vinblastine, Doxorubicin, | Breast |

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| | | | |
|-----------|-------------|---|--------|
| | | Thiotepa, Fluoxymesterone | |
| Rofecoxib | Bay-12-9566 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Bay-12-9566 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Bay-12-9566 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Bay-12-9566 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Bay-12-9566 | Etoposide, Carboplatin | Lung |
| Rofecoxib | Bay-12-9566 | Etoposide, Cisplatin | Lung |
| Rofecoxib | Bay-12-9566 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Bay-12-9566 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Bay-12-9566 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | Metastat | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | Metastat | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | Metastat | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | Metastat | Mitoxantrone, Flou | Breast |

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|-----------|------------|--|--------|
| | | Fluorouracil and Leucovorin | |
| Rofecoxib | Metastatic | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymesterone | Breast |
| Rofecoxib | Metastatic | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Metastatic | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | Metastatic | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | Metastatic | Fluorouracil, Levamisole | Colon |
| Rofecoxib | Metastatic | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | Metastatic | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | Metastatic | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | Metastatic | Etoposide, Carboplatin | Lung |
| Rofecoxib | Metastatic | Etoposide, Cisplatin | Lung |

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| | | | |
|-----------|----------|--|--------|
| Rofecoxib | Metastat | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | Metastat | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | Metastat | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | D-2163 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | D-2163 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | D-2163 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | D-2163 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| Rofecoxib | D-2163 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | D-2163 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | D-2163 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | D-2163 | Vinblastine, Doxorubicin, Thiotepa, | Breast |

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| | | | |
|-----------|--------|---|--------|
| | | Fluoxymesterone | |
| Rofecoxib | D-2163 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | D-2163 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | D-2163 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | D-2163 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | D-2163 | Etoposide, Carboplatin | Lung |
| Rofecoxib | D-2163 | Etoposide, Cisplatin | Lung |
| Rofecoxib | D-2163 | Paclitaxel, Carboplatin | Lung |
| Rofecoxib | D-2163 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | D-2163 | Paclitaxel, Cisplatin | Lung |
| Rofecoxib | D-1927 | Doxorubicin and Cyclophosphamide | Breast |
| Rofecoxib | D-1927 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| Rofecoxib | D-1927 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| Rofecoxib | D-1927 | Mitoxantrone, Flou rouracil and | Breast |

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| | | | |
|-----------|--------|---|--------|
| | | Leucovorin | |
| Rofecoxib | D-1927 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| Rofecoxib | D-1927 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | D-1927 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| Rofecoxib | D-1927 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| Rofecoxib | D-1927 | Fluorouracil, Levamisole | Colon |
| Rofecoxib | D-1927 | Leucovorin, Fluorouracil | Colon |
| Rofecoxib | D-1927 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| Rofecoxib | D-1927 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| Rofecoxib | D-1927 | Etoposide, Carboplatin | Lung |
| Rofecoxib | D-1927 | Etoposide, Cisplatin | Lung |
| Rofecoxib | D-1927 | Paclitaxel, | Lung |

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| | | | |
|-----------|-------------|--|--------|
| | | Carboplatin | |
| Rofecoxib | D-1927 | Gemcitabine, Cisplatin | Lung |
| Rofecoxib | D-1927 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Compound M1 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | Compound M1 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Compound M1 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Compound M1 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| JTE-522 | Compound M1 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | Compound M1 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M1 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M1 | Vinblastine, Doxorubicin, Thiotepa, | Breast |

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| | | | |
|---------|-------------|---|--------|
| | | Fluoxymesterone | |
| JTE-522 | Compound M1 | Fluorouracil, Levamisole | Colon |
| JTE-522 | Compound M1 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Compound M1 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Compound M1 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Compound M1 | Etoposide, Carboplatin | Lung |
| JTE-522 | Compound M1 | Etoposide, Cisplatin | Lung |
| JTE-522 | Compound M1 | Paclitaxel, Carboplatin | Lung |
| JTE-522 | Compound M1 | Gemcitabine, Cisplatin | Lung |
| JTE-522 | Compound M1 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Compound M2 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | Compound M2 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Compound M2 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Compound M2 | Mitoxantrone, Fluorouracil and | Breast |

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| | | | |
|---------|-------------|---|--------|
| | | Leucovorin | |
| JTE-522 | Compound M2 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | Compound M2 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M2 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M2 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | Compound M2 | Fluorouracil, Levamisole | Colon |
| JTE-522 | Compound M2 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Compound M2 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Compound M2 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Compound M2 | Etoposide, Carboplatin | Lung |
| JTE-522 | Compound M2 | Etoposide, Cisplatin | Lung |
| JTE-522 | Compound M2 | Paclitaxel, | Lung |

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| | | | |
|---------|-------------|--|--------|
| | | Carboplatin | |
| JTE-522 | Compound M2 | Gemcitabine, Cisplatin | Lung |
| JTE-522 | Compound M2 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Compound M3 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | Compound M3 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Compound M3 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Compound M3 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| JTE-522 | Compound M3 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | Compound M3 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M3 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M3 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |

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| | | | |
|---------|-------------|---|--------|
| JTE-522 | Compound M3 | Fluorouracil, Levamisole | Colon |
| JTE-522 | Compound M3 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Compound M3 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Compound M3 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Compound M3 | Etoposide, Carboplatin | Lung |
| JTE-522 | Compound M3 | Etoposide, Cisplatin | Lung |
| JTE-522 | Compound M3 | Paclitaxel, Carboplatin | Lung |
| JTE-522 | Compound M3 | Gemcitabine, Cisplatin | Lung |
| JTE-522 | Compound M3 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Compound M4 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | Compound M4 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Compound M4 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Compound M4 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |

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| | | | |
|---------|-------------|---|--------|
| JTE-522 | Compound M4 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | Compound M4 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M4 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M4 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | Compound M4 | Fluorouracil, Levamisole | Colon |
| JTE-522 | Compound M4 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Compound M4 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Compound M4 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Compound M4 | Etoposide, Carboplatin | Lung |
| JTE-522 | Compound M4 | Etoposide, Cisplatin | Lung |
| JTE-522 | Compound M4 | Paclitaxel, Carboplatin | Lung |

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| | | | |
|---------|-------------|--|--------|
| JTE-522 | Compound M4 | Gemcitabine, Cisplatin | Lung |
| JTE-522 | Compound M4 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Compound M5 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | Compound M5 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Compound M5 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Compound M5 | Mitoxantrone, Fluorouracil and Leucovorin | Breast |
| JTE-522 | Compound M5 | Vinblastine, Doxorubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | Compound M5 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M5 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M5 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | Compound M5 | Fluorouracil, | Colon |

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| | | | |
|---------|-------------|--|--------|
| | | ubicin, Thiotepa, and Fluoxymestrone | |
| JTE-522 | Compound M7 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M7 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Compound M7 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | Compound M7 | Fluorouracil, Levamisole | Colon |
| JTE-522 | Compound M7 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Compound M7 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Compound M7 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Compound M7 | Etoposide, Carboplatin | Lung |
| JTE-522 | Compound M7 | Etoposide, Cisplatin | Lung |
| JTE-522 | Compound M7 | Paclitaxel, Carboplatin | Lung |
| JTE-522 | Compound M7 | Gemcitabine, | Lung |

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| | | | |
|---------|-------------|--|--------|
| | | Cisplatin | |
| JTE-522 | Compound M7 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Bay-12-9566 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | Bay-12-9566 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Bay-12-9566 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Bay-12-9566 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| JTE-522 | Bay-12-9566 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | Bay-12-9566 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Bay-12-9566 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Bay-12-9566 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | Bay-12-9566 | Fluorouracil, Levamisole | Colon |

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| | | | |
|---------|-------------|---|--------|
| JTE-522 | Bay-12-9566 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Bay-12-9566 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Bay-12-9566 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Bay-12-9566 | Etoposide, Carboplatin | Lung |
| JTE-522 | Bay-12-9566 | Etoposide, Cisplatin | Lung |
| JTE-522 | Bay-12-9566 | Paclitaxel, Carboplatin | Lung |
| JTE-522 | Bay-12-9566 | Gemcitabine, Cisplatin | Lung |
| JTE-522 | Bay-12-9566 | Paclitaxel, Cisplatin | Lung |
| JTE-522 | Metastat | Doxorubicin and Cyclophasphamide | Breast |
| JTE-522 | Metastat | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | Metastat | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | Metastat | Mitoxantrone,Flou rouracil and Leucovorin | Breast |
| JTE-522 | Metastat | Vinblastine,Doxor ubicin, Thiotepa, | Breast |

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| | | | |
|---------|----------|--|--------|
| | | and Fluoxymestrone | |
| JTE-522 | Metastat | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Metastat | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | Metastat | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | Metastat | Fluorouracil, Levamisole | Colon |
| JTE-522 | Metastat | Leucovorin, Fluorouracil | Colon |
| JTE-522 | Metastat | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | Metastat | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | Metastat | Etoposide, Carboplatin | Lung |
| JTE-522 | Metastat | Etoposide, Cisplatin | Lung |
| JTE-522 | Metastat | Paclitaxel, Carboplatin | Lung |
| JTE-522 | Metastat | Gemcitabine, Cisplatin | Lung |

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| | | | |
|---------|----------|--|--------|
| JTE-522 | Metastat | Paclitaxel, Cisplatin | Lung |
| JTE-522 | D-2163 | Doxorubicin and Cyclophosphamide | Breast |
| JTE-522 | D-2163 | Cyclophosphamide, Doxorubicin, and Fluorouracil | Breast |
| JTE-522 | D-2163 | Cyclophosphamide, Fluorouracil and Mitoxantrone | Breast |
| JTE-522 | D-2163 | Mitoxantrone, Flou rouracil and Leucovorin | Breast |
| JTE-522 | D-2163 | Vinblastine, Doxor ubicin, Thiotepa, and Fluoxymestrone | Breast |
| JTE-522 | D-2163 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | D-2163 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | D-2163 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | D-2163 | Fluorouracil, Levamisole | Colon |
| JTE-522 | D-2163 | Leucovorin, | Colon |

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| | | | |
|---------|--------|--|--|
| | | Fluorouracil | |
| JTE-522 | D-2163 | Cyclophosphamide, Lung Doxorubicin, Etoposide | |
| JTE-522 | D-2163 | Cyclophosphamide, Lung Doxorubicin, Vincristine | |
| JTE-522 | D-2163 | Etoposide, Lung Carboplatin | |
| JTE-522 | D-2163 | Etoposide, Lung Cisplatin | |
| JTE-522 | D-2163 | Paclitaxel, Lung Carboplatin | |
| JTE-522 | D-2163 | Gemcitabine, Lung Cisplatin | |
| JTE-522 | D-2163 | Paclitaxel, Lung Cisplatin | |
| JTE-522 | D-1927 | Doxorubicin and Breast Cyclophasphamide | |
| JTE-522 | D-1927 | Cyclophosphamide, Breast Doxorubicin, and Fluorouracil | |
| JTE-522 | D-1927 | Cyclophosphamide, Breast Fluorouracil and Mitoxantrone | |
| JTE-522 | D-1927 | Mitoxantrone, Flou Breast rouracil and Leucovorin | |
| JTE-522 | D-1927 | Vinblastine, Doxor Breast ubicin, Thiotepa, and | |

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| | | | |
|---------|--------|--|--------|
| | | Fluoxymestrone | |
| JTE-522 | D-1927 | Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | D-1927 | Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil | Breast |
| JTE-522 | D-1927 | Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone | Breast |
| JTE-522 | D-1927 | Fluorouracil, Levamisole | Colon |
| JTE-522 | D-1927 | Leucovorin, Fluorouracil | Colon |
| JTE-522 | D-1927 | Cyclophosphamide, Doxorubicin, Etoposide | Lung |
| JTE-522 | D-1927 | Cyclophosphamide, Doxorubicin, Vincristine | Lung |
| JTE-522 | D-1927 | Etoposide, Carboplatin | Lung |
| JTE-522 | D-1927 | Etoposide, Cisplatin | Lung |
| JTE-522 | D-1927 | Paclitaxel, Carboplatin | Lung |
| JTE-522 | D-1927 | Gemcitabine, Cisplatin | Lung |
| JTE-522 | D-1927 | Paclitaxel, | Lung |

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| |
|-----------|
| Cisplatin |
|-----------|

Biological EvaluationCOX-2 Inhibitors

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1. Lewis Lung Model:

Mice were injected subcutaneously in the left paw (1 x 10⁶ tumor cells suspended in 30 % Matrigel) and tumor volume was evaluated using a phlethysmometer twice a week for 30-60 days. Blood was drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data are expressed as the mean +/- SEM. Student's and Mann-Whitney tests were used to assess differences between means using the InStat software package. Celecoxib given in the diet at doses between 160-3200 ppm retarded the growth of these tumors. The inhibitory effect of celecoxib was dose-dependent and ranged from 48 % to 85 % as compared with the control tumors.

Analysis of lung metastasis was done in all the animals by counting metastasis in a stereomicroscope and by histochemical analysis of consecutive lung sections. Celecoxib did not affect lung metastasis at the lower dose of 160 ppm, however surface metastasis was reduced by more than 50 % when given at doses between 480-3200 ppm. In addition, histopathological analysis revealed that celecoxib dose-dependently reduced the size of the metastatic lesions in the lung.

2. HT-29 Model:

Mice were injected subcutaneously in the left paw (1 x 10⁶ tumor cells suspended in 30 % Matrigel) and tumor volume was evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of human colon cancer cells (HT-29) into nude mice produces tumors that will reach 0.6-2 ml between 30-50 days. Blood was drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data are expressed as the mean +/- SEM. Student's and Mann-Whitney tests were used to assess differences between means using the InStat software package.

A. Mice injected with HT-29 cancer cells were treated with cytoxin i.p at doses of 50 mg/kg on days 5,7 and 9 in the presence or absence of celecoxib in the diet. The efficacy of both agents were determined by measuring tumor volume. Treatment using a celecoxib related COX-2 inhibitor (SC-58236) reduced tumor volume by 89 %. In the same assay, indomethacin given at near the maximum tolerated dose of 2 mg/kg/day in the drinking water inhibited tumor formation by 77%. Moreover, the COX-2 selective inhibitor completely inhibited the formation of lung metastasis while the non-selective NSAID indomethacin was ineffective. The results from these studies demonstrate that celecoxib administered in the diet to tumor bearing mice can delay the growth of tumors and metastasis when administered as sole therapy. Moreover, a positive benefit is observed when celecoxib is administered in combination with a cytotoxic agent such as cyclophosphamide.

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B. In a second assay, mice injected with HT-29 cancer cells were treated with 5-FU on days 12 through 15. Mice injected with HT-29 cancer cells were treated with 5-FU i.p at doses of 50 mg/kg on days 12, 13, 14, and 15 in the presence or absence of celecoxib in the diet. The efficacy of both agents were determined by measuring tumor volume. Treatment using a celecoxib reduced tumor volume by 68 %. In the same assay, 5-FU decreased tumor volume by 61%. Further, the combination of celecoxib and 5-FU decreased tumor volume by 83%.

C. In a third assay, mice injected with HT-29 colon cancer cells were treated with 5-FU i.p 50 mg/kg on days 14 through 17 in the presence or absence of celecoxib (1600ppm) and valdecoxib (160 ppm) in the diet. The efficacy of both agents were determined by measuring tumor volume. Treatment with 5-FU resulted in a 35% reduction in tumor volume. Treatment with celecoxib and valdecoxib reduced tumor volume by 52 % and 69 %, respectively. In the same assay, the combination of 5-FU and celecoxib decreased tumor volume by 72 % while the combination of 5-FU and valdecoxib decreased tumor volume by 74b % (Table 25).

Table 25. Tumor Volume Effect of Celecoxib and Valdecoxib alone and in combination with 5-Fluorouracil.

| Days | Vehicle | 5FU 50mpk | celecoxib 160ppm | celecoxib 160ppm /5FU 50mpk | valdecoxib 160ppm | valdecoxib 160ppm/ 5FU 50mpk |
|------|---------|--------------|---------------------|--------------------------------------|----------------------|---------------------------------------|
|------|---------|--------------|---------------------|--------------------------------------|----------------------|---------------------------------------|

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|----|------|------|------|------|------|------|
| 11 | 0.04 | 0.05 | 0.05 | 0.05 | 0.06 | 0.06 |
| 14 | 0.13 | 0.12 | 0.13 | 0.13 | 0.13 | 0.13 |
| 18 | 0.19 | 0.16 | 0.17 | 0.14 | 0.17 | 0.16 |
| 21 | 0.23 | 0.21 | 0.2 | 0.17 | 0.2 | 0.19 |
| 28 | 0.38 | 0.3 | 0.25 | 0.22 | 0.25 | 0.21 |
| 35 | 0.62 | 0.46 | 0.35 | 0.28 | 0.32 | 0.29 |
| 42 | 1.01 | 0.68 | 0.52 | 0.32 | 0.36 | 0.31 |

Volume (ml)

D. In a fourth assay, mice injected with HT-29 colon cancer cells were treated with celecoxib (10, 40 or 160 ppm) in the diet beginning at day 10. An approximate dose dependent effect was observed. (Table 26).

Table 26. Celecoxib Inhibits HT-29 Human Colon Carcinoma

| Days | vehicle | 10 ppm | 40 ppm | 160 ppm |
|------|---------|--------|--------|---------|
| 14 | 0.114 | 0.124 | 0.125 | 0.120 |
| 22 | 0.25 | 0.25 | 0.19 | 0.14 |
| 28 | 0.45 | 0.36 | 0.27 | 0.21 |
| 35 | 0.79 | 0.57 | 0.4 | 0.3 |
| 42 | 1.38 | 0.89 | 0.68 | 0.49 |
| 50 | 1.9 | 1.49 | 1.04 | 0.8 |

Volume (ml)

MMP Inhibitors

1. Pancreatic Cell (PC-3) Model:

In this study, the test groups were a vehicle control, Compound M14, Compound M14 with cisplatin and cisplatin alone with n=10 for each group. The tumors

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were measured with a caliper and the volume calculated using the formula for the volume of an elipsoid. The cisplatin dose was 10 mpk administered by the intraperitoneal route on day 8 post injection of tumor cells Compound M14, 50 mpk, was first administered about 6:00 pm the evening of the same day that the tumor cells were injected in the morning. The same dose of Compound M14 was administered bid for each following day. Tumor volume (mm^3) was measured on day 25. The data below clearly show an improved response with the combination of the MMP inhibitor and cisplatin.

| PC3 Model MMP Inhibitor Combination Study Results | |
|--|---|
| Agent Administered PC3 Model | Tumor Volume at Day 25 (mm^3) |
| vehicle | 860 |
| cisplatin | 630 |
| Compound M14 | 480 |
| Compound M14 with cisplatin | 110 |

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2. Breast Tumor Model:

This study was carried out essentially as PC-3 model. MX-1 breast tumor pieces were implanted (with a trocar) into nude mice with n=10 per group. Dosing with Compound M14 (10 mpk or 50 mpk, PO bid) was initiated when the tumors reached a size of 60-120 mg. Dosing was continued for 26 days. Taxol was administered at a dose of 9 mpk for the first five days following the start of dosing by the interperitoneal route. The tumors were measured using a caliper and the volume calculated using the formula for the volume of an elipsoid. The results tabulated below clearly show an improved response with combination therapy. An improved response is obtained with lower doses Compound M14.

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| MX-1 Model MMP Inhibitor Combination Study Results | |
|---|--|
| Agent Administered | Tumor Volume at Day 25 (mm ³) |
| vehicle | 1920 |
| taxol | 1280 |
| Compound M14 @ 10 mpk | 960 |

-310-

| | |
|--|------|
| Compound M14 @ 50 mpk | 1260 |
| Compound M14 @ 50 mpk + taxol @ 9 mpk | 480 |
| Compound M14 @ 10 mpk + taxol @ 9 mpk | 240 |

3. MX-1 Adjuvant Model:

Mice were implanted with MX-1 tumors and allowed to grow to 50 - 100 mm³. The animals were dosed with cyclophosphamide (100 or 80 mpk). This was considered Day 1. Two weeks later the animals were pair matched after tumor regression and dosing BID with the MMPI was begun until the end of the experiment. Tumors were measured weekly. The endpoint for the study was a final tumor size of 1.5 g.

| | Cycloph- osfamide Dose (mpk) | MMPI | MMPI Dose (mpk) | MDS | sem |
|------------------|---------------------------------------|--------------|-----------------------|------|-----|
| saline | | | | 23.9 | 1.3 |
| cyclophosphamide | 100 | | | 39.5 | 1.2 |
| cyclophosphamide | 80 | | | 37.2 | 1.5 |
| cyclophosphamide | 100 | Compound M14 | 200 | 52.7 | 2.9 |
| cyclophosphamide | 100 | Compound M14 | 50 | 43.7 | 1.6 |
| cyclophosphamide | 80 | Compound M14 | 200 | 53.9 | 2.9 |
| cyclophosphamide | 80 | Compound M14 | 50 | 44.2 | 1.8 |

MDS = mean days to tumor weight of 1.5 g

-311-

4. MX-1 breast tumor with taxol:

Mice were implanted with MX-1 tumors and allowed to grow to 50 - 100 mg. The animals were pair matched and this was considered Day 1. Treatment with MMPI was begun BID on Day 1 until the end of the experiment. Taxol was injected IP (15 or 9 mpk) QD for 5 days (days 1 -5). Tumors were measured weekly until an endpoint of 1.5 g was reached.

10

| | Taxol Dose (mpk) | MMPI | MMPI Dose (mpk) | MDS | sem |
|--------------|------------------------|-----------------|-----------------------|------|-----|
| vehicle | | | | 25.3 | 0.8 |
| mmpi | | Compound M14 | 100 | 32.2 | 2.8 |
| mmpi | | Compound M14 | 20 | 34.7 | 3 |
| taxol + mmpi | 18 | Compound M14 | | 56 | 11 |
| taxol + mmpi | 9 | Compound M14 | | 30.1 | 1.8 |
| taxol + mmpi | 18 | Compound M14 | 100 | 61 | |
| taxol + mmpi | 9 | Compound M14 | 100 | 46.7 | 3.7 |
| taxol + mmpi | 18 | Compound M14 | 20 | 59.3 | 7 |
| taxol + mmpi | 9 | Compound M14 | 20 | 39.3 | 1.9 |

MDS = 1.5 g

15 5. SK-mes tumor with Taxol

Mice were implanted with SK-mes tumors and allowed to grow to 50 - 100 mg. The animals were pair matched and this was considered Day 1. Treatment with MMPI was begun BID on Day 1 until the end of the experiment. Taxol was injected IP (18 or 9 mpk) QD for 5 days (days

20

-312-

1 -5). Tumors were measured weekly until an endpoint of 1.0 g was reached.

| | Taxol Dose (mpk) | MMPI | MMPI Dose (mpk) | MDS | sem |
|--------------|------------------------|-----------------|-----------------------|------|-----|
| vehicle | | | | 21.2 | 2.1 |
| mmpi | | Compound M14 | 100 | 24.7 | 1.6 |
| mmpi | | Compound M14 | 20 | 18 | 1.1 |
| taxol | 18 | | | 31.5 | 2.4 |
| taxol | 9 | | | 26.1 | 2.3 |
| taxol + mmpi | 18 | Compound M14 | 100 | 43 | 4 |
| taxol + mmpi | 9 | Compound M14 | 100 | 34.8 | 1.9 |
| taxol + mmpi | 18 | Compound M14 | 20 | 39.5 | 3.6 |
| taxol + mmpi | 9 | Compound M14 | 20 | 34.1 | 5.7 |

MDS = 1.0 g

5 6. HT-29 tumor with Irinotecan

Mice were implanted with HT-29 tumors and allowed to grow to 50 - 100 mg. The animals were pair matched and this was considered Day 1. Treatment with MMPI was
 10 begun BID on Day 1 until the end of the experiment. Irinotecan was injected IP (100 or 50 mpk) QD for 5 days (days 1-5). Tumors were measured weekly until an endpoint of 1.0 g was reached.

| | Irinotecan Dose (mpk) | MMPI | MMPI Dose (mpk) | MDS | SEM |
|--------------|-----------------------------|-----------------|-----------------------|------|-----|
| vehicle | | | | 36.4 | 4.3 |
| mmpi | | Compound M14 | 100 | 37.9 | 5.0 |
| mmpi | | Compound M14 | 20 | 36 | 4.2 |
| Irinotecan | 100 | | | 36.7 | 2.6 |
| Irinotecan | 50 | | | 38.1 | 3.0 |
| Irinotecan + | 100 | Compound | 100 | 51.4 | 4.4 |

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| | | | | | |
|----------------------|-----|-----------------|-----|------|-----|
| mmpi | | M14 | | | |
| Irinotecan + mmpi | 50 | Compound M14 | 100 | 44.4 | 4.0 |
| Irinotecan + mmpi | 100 | Compound M14 | 20 | 40.6 | 4.7 |
| Irinotecan + mmpi | 50 | Compound M14 | 20 | 36.1 | 3.0 |

MDS = 1.0 g

What is claimed is:

1. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment
 5 or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor, and an antineoplastic agent, wherein said antineoplastic agent is selected
 10 from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol,
 15 leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and
 20 eflornithine (DFMO).

2. The method of Claim 1 wherein the combination is administered in a sequential manner.

25 3. The method of Claim 1 wherein the combination is administered in a substantially simultaneous manner.

4. The method of Claim 1 wherein the antineoplastic agent is capecitabine.

-315-

5. The method of Claim 1 wherein the antineoplastic agent is carboplatin.

6. The method of Claim 1 wherein the
5 antineoplastic agent is cisplatin.

7. The method of Claim 1 wherein the antineoplastic agent is Cell Pathways CP-461.

10 8. The method of Claim 1 wherein the antineoplastic agent is docetaxel.

9. The method of Claim 1 wherein the antineoplastic agent is doxorubicin.

15

10. The method of Claim 1 wherein the antineoplastic agent is etoposide.

11. The method of Claim 1 wherein the
20 antineoplastic agent is fluoxymestrine.

12. The method of Claim 1 wherein the antineoplastic agent is gemcitabine.

25 13. The method of Claim 1 wherein the antineoplastic agent is goserelin.

14. The method of Claim 1 wherein the antineoplastic agent is irinotecan.

30

15. The method of Claim 1 wherein the antineoplastic agent is ketoconazole.

-316-

16. The method of Claim 1 wherein the antineoplastic agent is letrozol.

5 17. The method of Claim 1 wherein the antineoplastic agent is leucovorin.

18. The method of Claim 1 wherein the antineoplastic agent is levamisole.

10

19. The method of Claim 1 wherein the antineoplastic agent is megestrol.

20. The method of Claim 1 wherein the antineoplastic agent is mitoxantrone.

15

21. The method of Claim 1 wherein the antineoplastic agent is paclitaxel.

22. The method of Claim 1 wherein the antineoplastic agent is raloxifene.

20

23. The method of Claim 1 wherein the antineoplastic agent is retinoic acid.

25

24. The method of Claim 1 wherein the antineoplastic agent is tamoxifen.

25. The method of Claim 1 wherein the antineoplastic agent is thiotepa.

30

26. The method of Claim 1 wherein the antineoplastic agent is topotecan.

27. The method of Claim 1 wherein the
5 antineoplastic agent is toremifene.

28. The method of Claim 1 wherein the antineoplastic agent is vinorelbine.

10 29. The method of Claim 1 wherein the antineoplastic agent is vinblastine.

30. The method of Claim 1 wherein the antineoplastic agent is vincristine.

15

31. The method of Claim 1 wherein the antineoplastic agent is selenium (selenomethionine).

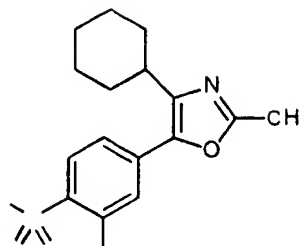
32. The method of Claim 1 wherein the
20 antineoplastic agent is sulindac sulfone.

33. The method of Claim 1 wherein the antineoplastic agent is eflornithine (DFMO).

25 34. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

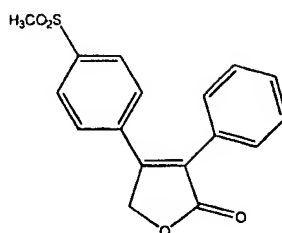
-318-

1)



-319-

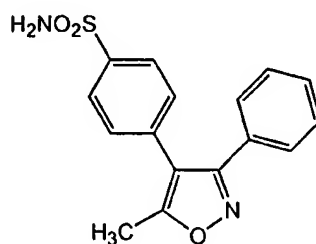
5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

5

6)



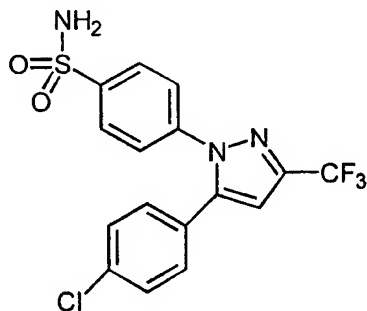
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7) N-[[4-(5-methyl-3-phenylisoxazol-

10

4yl]phenyl]sulfonyl]propanamide,

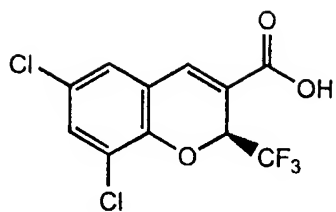
8)



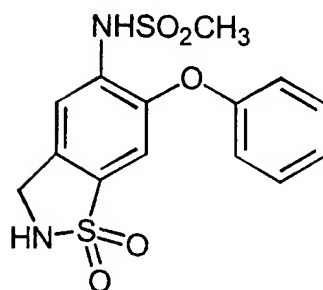
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

-320-

9)

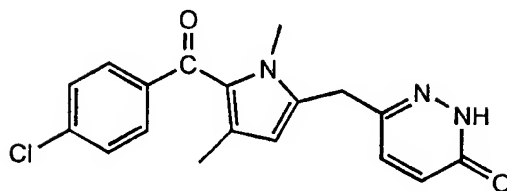


10)



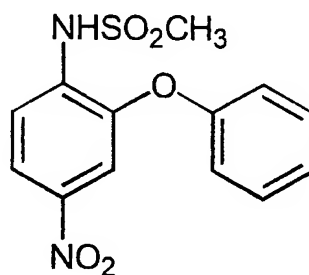
5

11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

12)

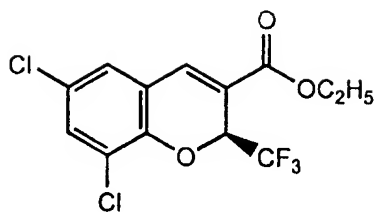


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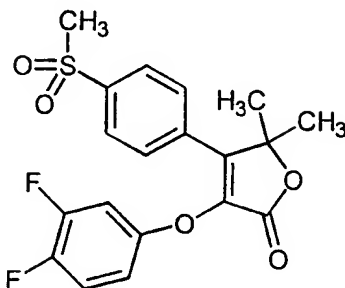
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

-321-

13)



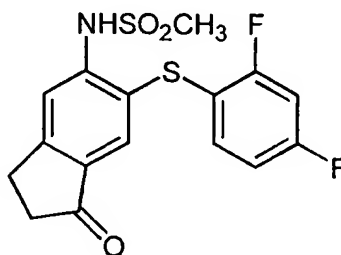
14)



5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

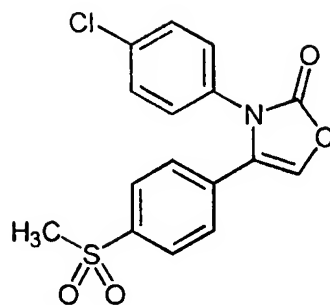
15)



10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

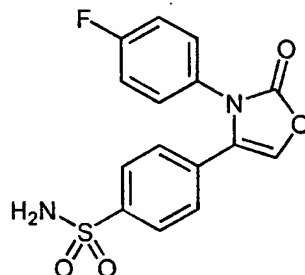
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

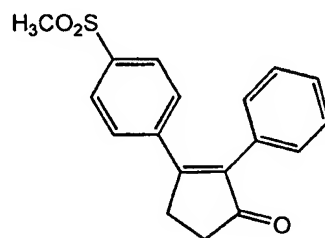
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17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

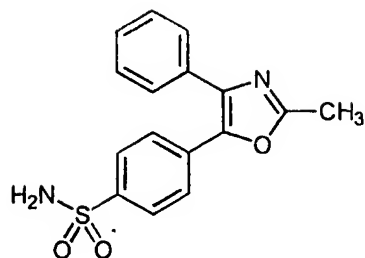


10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

-323-

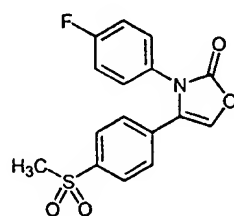
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

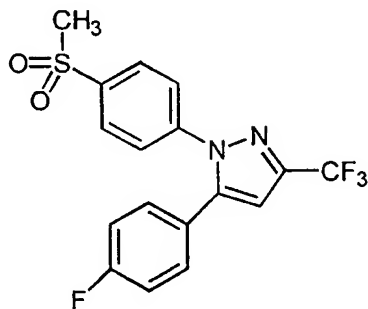
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20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

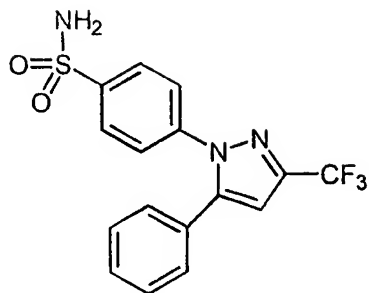


10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-324-

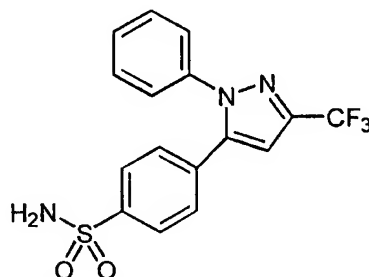
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

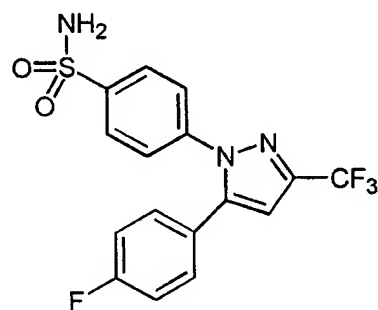
5

23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

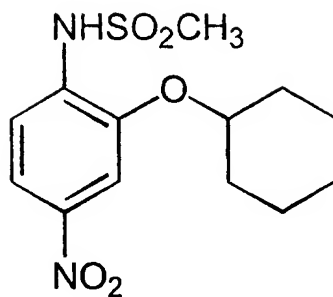


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4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

-325-

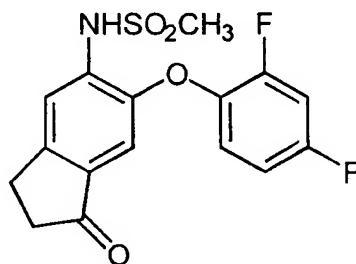
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

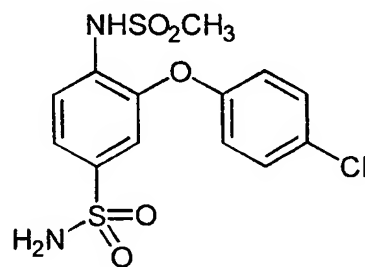
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26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

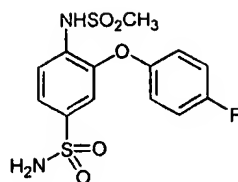
27)



10

3-(4-chlorophenoxy)-4-[(methanesulfonyl)amino]benzenesulfonamide,

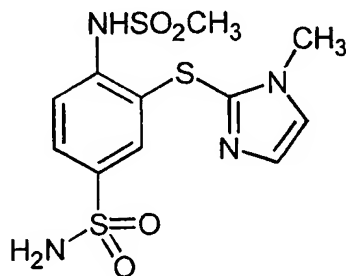
28)



3-(4-fluorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide,

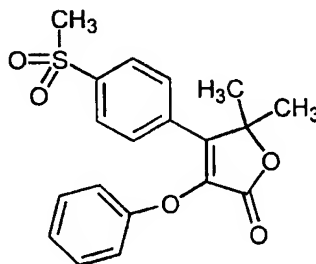
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29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4-
[(methylsulfonyl)amino]benzenesulfonamide,

30)

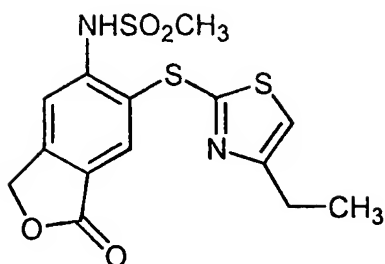


10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-
phenoxy-2(5H)-furanone,

327-

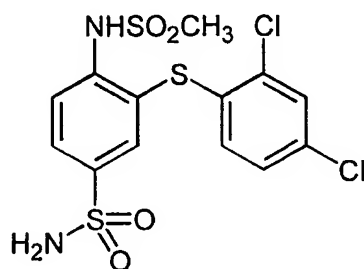
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

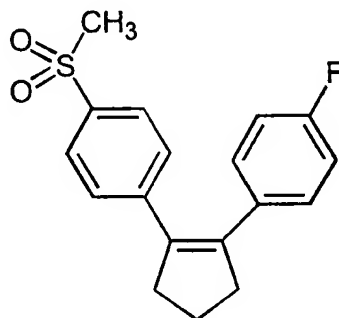
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32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

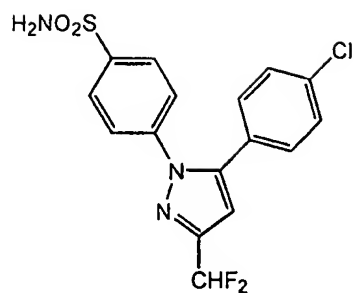


10

1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

-328-

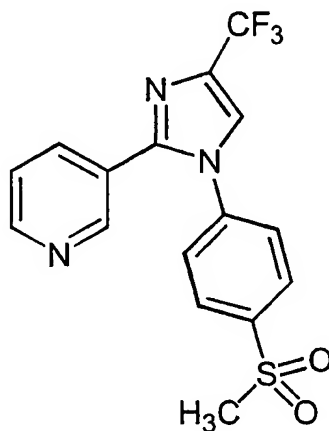
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

5

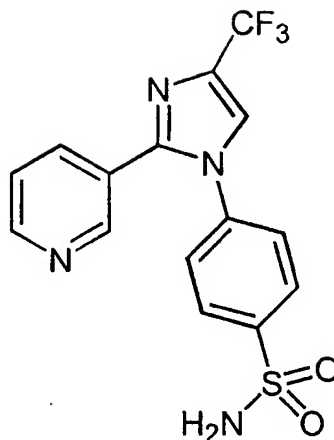
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-329-

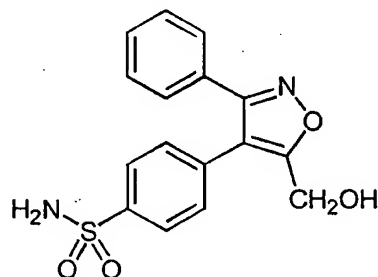
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

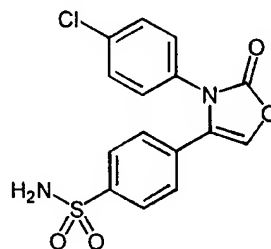
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37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

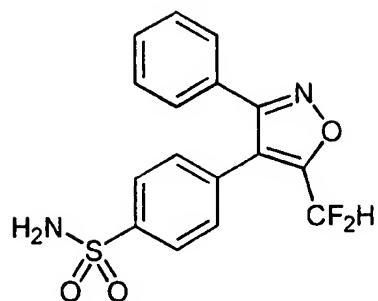
38)



4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

10

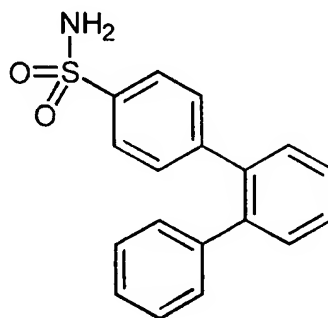
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

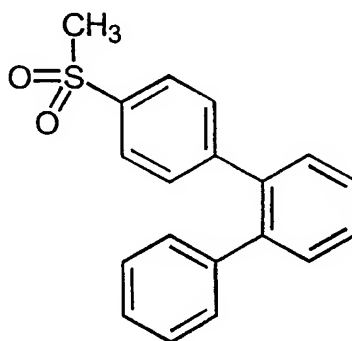
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40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

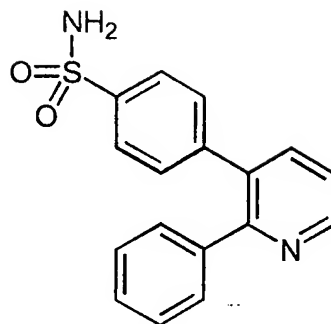


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4-(methylsulfonyl)-1,1',2,1''-terphenyl,

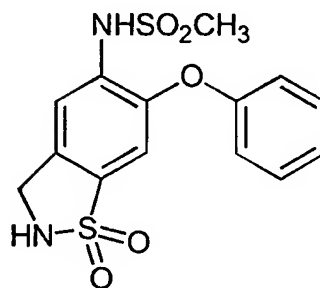
-331-

42)



4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

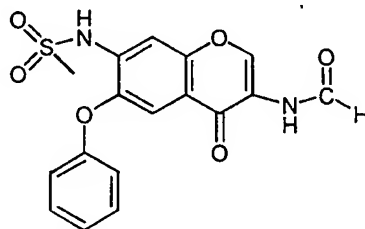
43)



5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

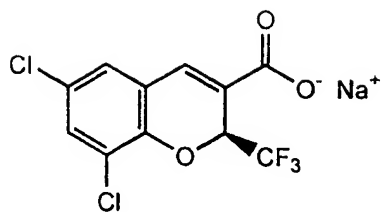


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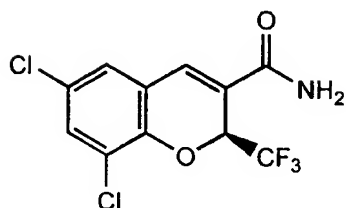
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-332-

45)

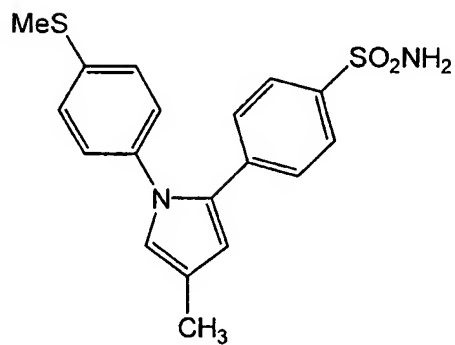


46)



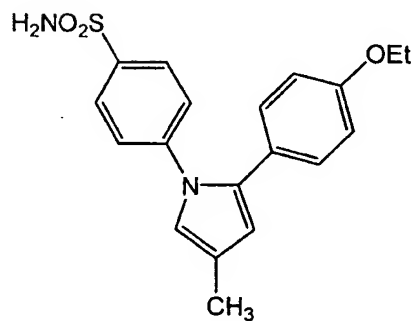
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47)



, and

48)

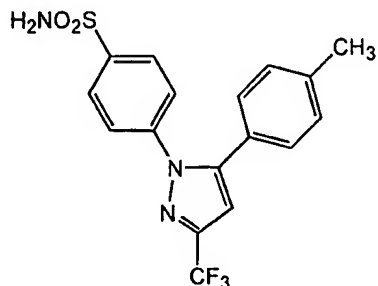


35. The method of Claim 1 wherein the
 10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

-333-

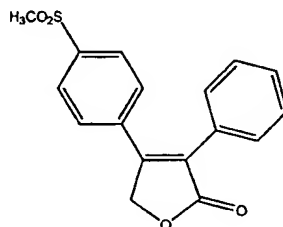
36. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

37. The method of Claim 1 wherein the
5 cyclooxygenase-2 inhibitor is



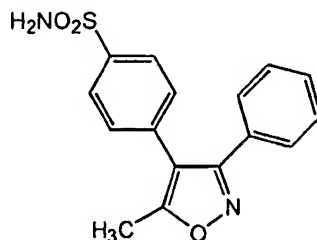
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

38. The method of Claim 1 wherein the
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

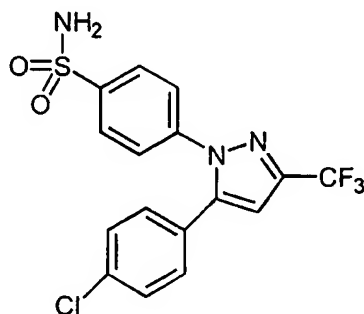
39. The method of Claim 1 wherein the
15 cyclooxygenase-2 inhibitor is



4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

40. The method of Claim 1 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide.

41. The method of Claim 1 wherein the
5 cyclooxygenase-2 inhibitor is



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

42. The method of Claim 1 wherein the neoplasia is
10 selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

43. The method of Claim 1 wherein the neoplasia is selected from the group consisting of acral lentiginous
15 melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma,
20 cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma,
25 fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma,

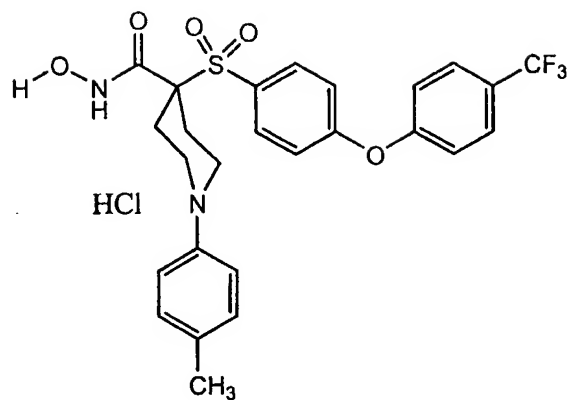
-335-

hemangiblastomas, hemangioendothelioma, hemangiomas,
hepatic adenoma, hepatic adenomatosis, hepatocellular
carcinoma, insulinoma, intraepithelial neoplasia,
interepithelial squamous cell neoplasia, invasive
5 squamous cell carcinoma, large cell carcinoma,
leiomyosarcoma, lentigo maligna melanomas, malignant
melanoma, malignant mesothelial tumors, medulloblastoma,
medulloepithelioma, melanoma, meningeal, mesothelial,
metastatic carcinoma, mucoepidermoid carcinoma,
10 neuroblastoma, neuroepithelial adenocarcinoma nodular
melanoma, oat cell carcinoma, oligodendroglial,
osteosarcoma, pancreatic polypeptide, papillary serous
adenocarcinoma, pineal cell, pituitary tumors,
plasmacytoma, pseudosarcoma, pulmonary blastoma, renal
15 cell carcinoma, retinoblastoma, rhabdomyosarcoma,
sarcoma, serous carcinoma, small cell carcinoma, soft
tissue carcinomas, somatostatin-secreting tumor,
squamous carcinoma, squamous cell carcinoma,
submesothelial, superficial spreading melanoma,
20 undifferentiated carcinoma, uveal melanoma, verrucous
carcinoma, vipoma, well differentiated carcinoma, and
Wilm's tumor.

44. The method of Claim 1 wherein the matrix
25 metalloproteinase inhibitor is selected from compounds,
and their pharmaceutically acceptable salts thereof, of
the group consisting of:

-336-

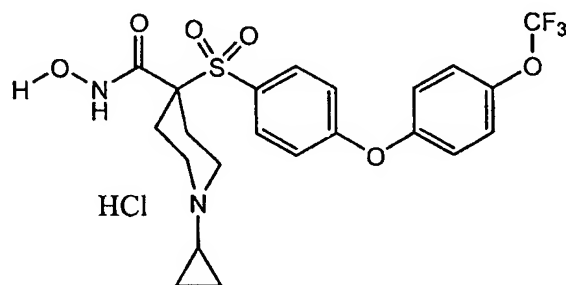
1)



N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

2)

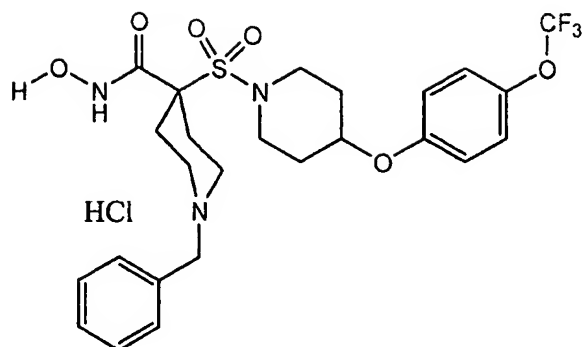


1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

10

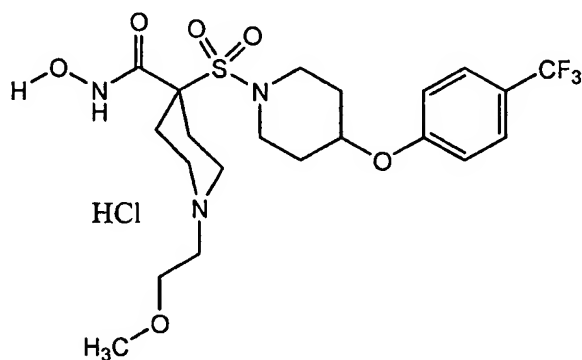
-337-

3)



N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

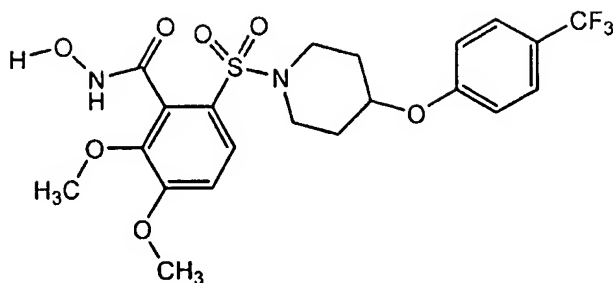
4)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

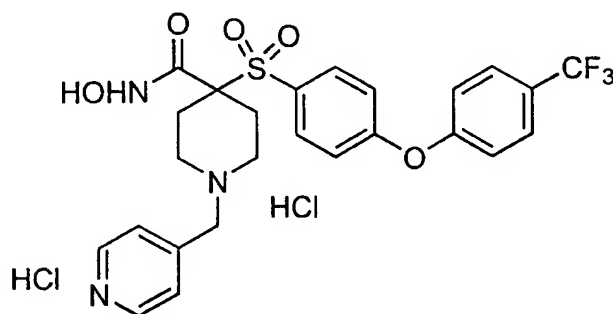
-338-

5)



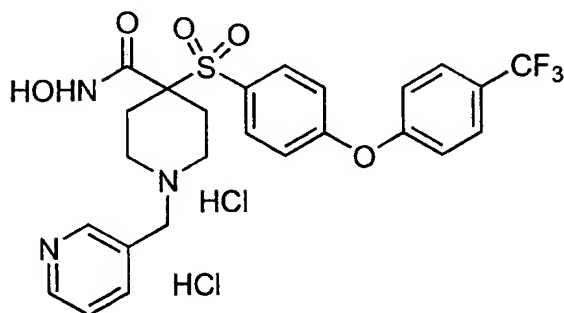
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

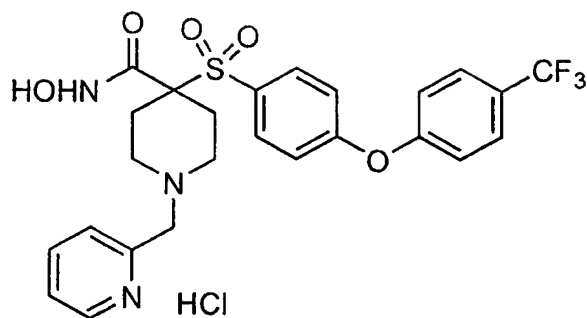
7)



N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

-339-

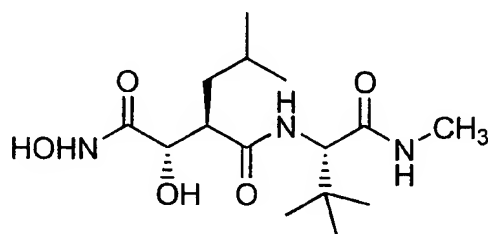
8)



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

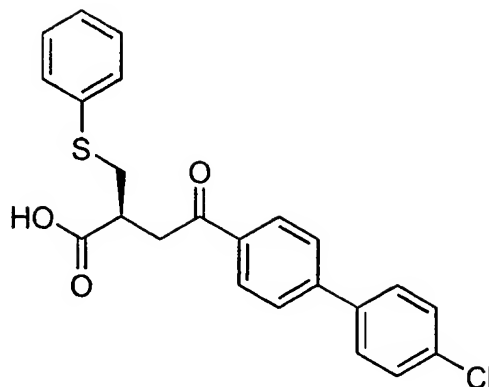


10

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-,

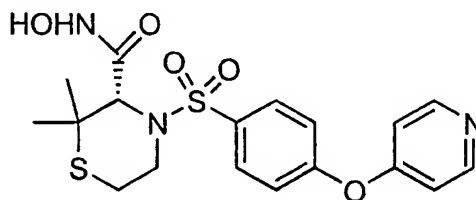
-340-

10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]-4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid,

11)



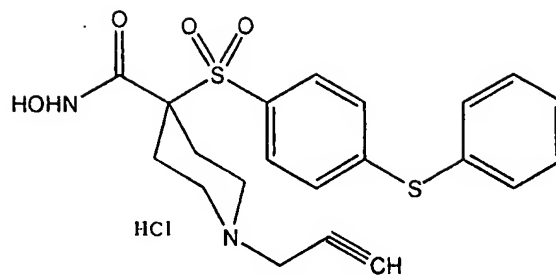
Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2
dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl] 3-
thiomorpholinecarboxamide,

12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
6-demethyl-6-deoxy-4-
dedimethylaminotetracycline,

13) Chiroscience D-2163, 2- [1S- [(2R,S)-
acetylmercapto- 5- phthalimido]pentanoyl- L-
leucyl)amino- 3- methylbutyl]imidazole,

-341-

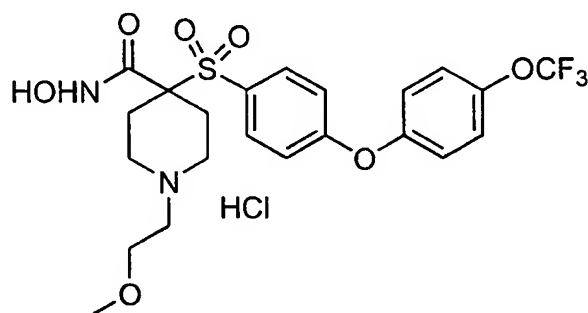
14)



N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide
monohydrochloride,

5

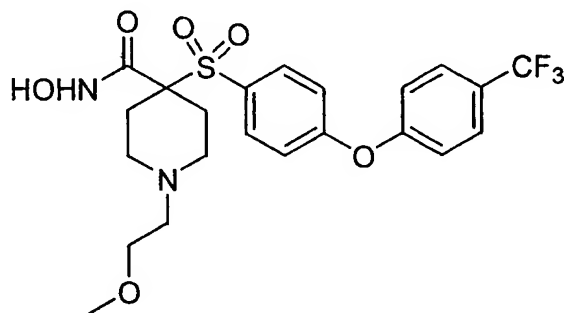
15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride,

10

16)

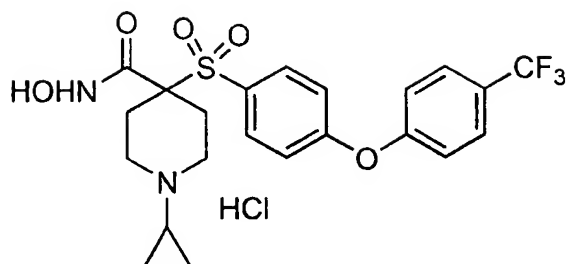


N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide,

15

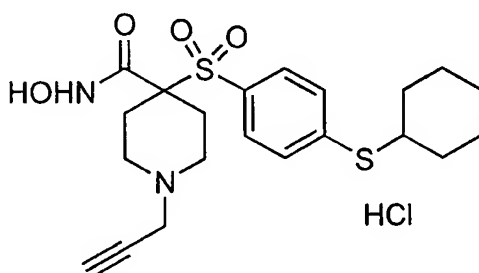
-342-

17)



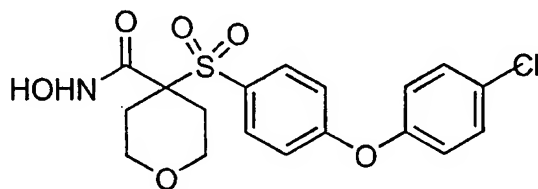
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

18)



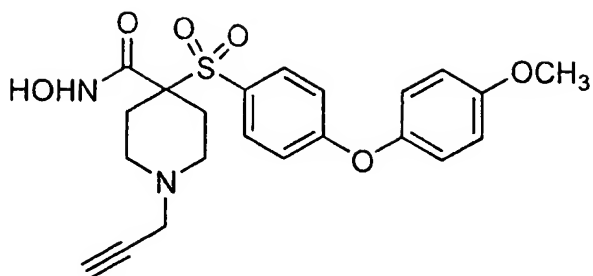
4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)



4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

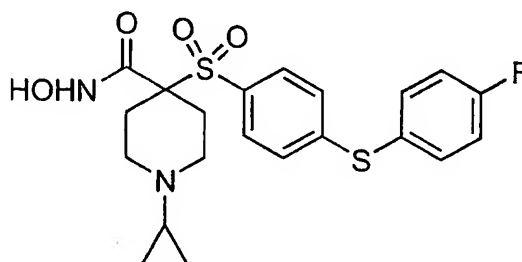
20)



N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

5

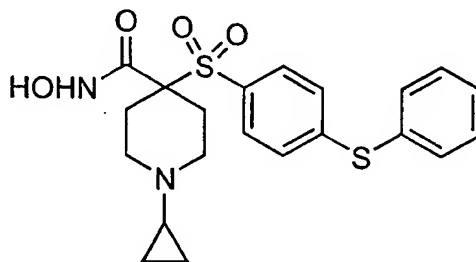
21)



1-cyclopropyl-4-[[4-(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

10

22)

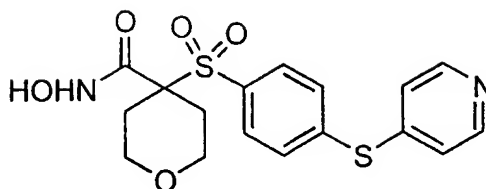


1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

15

-344-

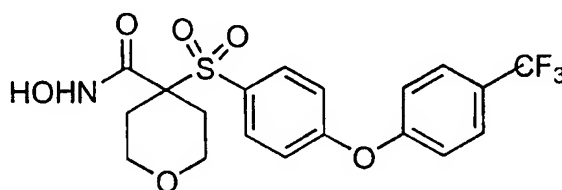
23)



tetrahydro-N-hydroxy-4-[[4-(4-
pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-
carboxamide, and

5

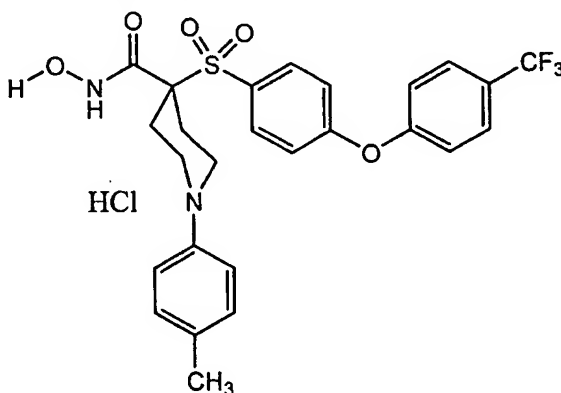
24)



tetrahydro-N-hydroxy-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-
pyran-4-carboxamide.

10

45. The method of Claim 1 wherein the matrix
metalloproteinase inhibitor is

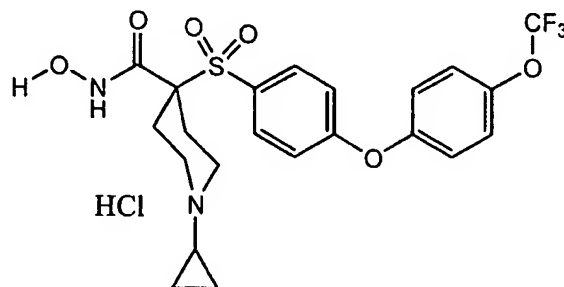


N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride.

15

-345-

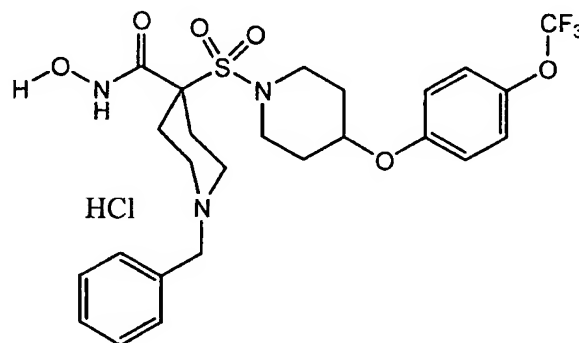
46. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

47. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

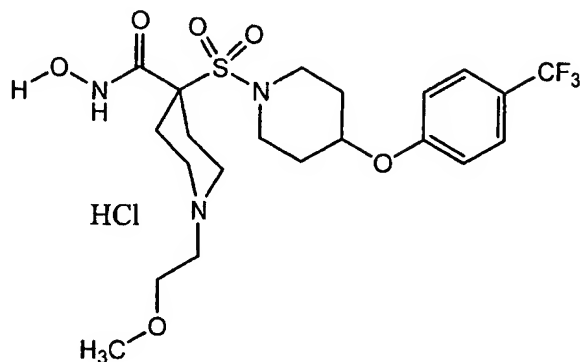


10

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

-346-

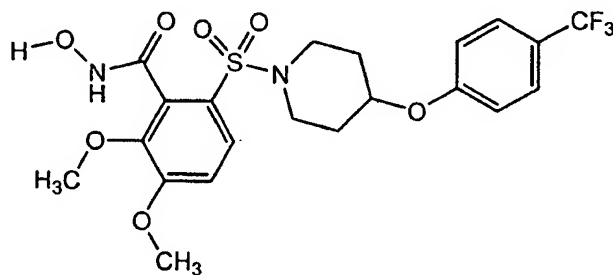
48. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-piperidinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

49. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

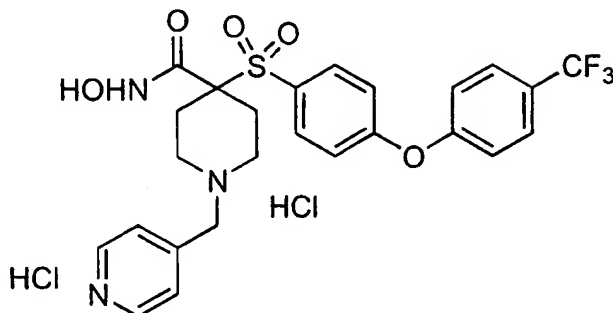
10



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

-347-

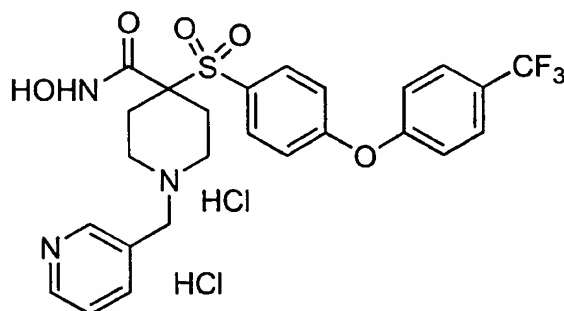
50. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

51. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

10

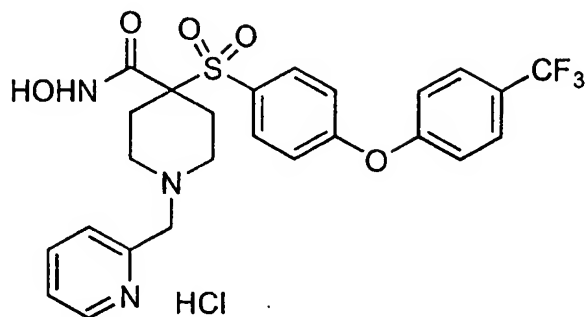


15

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

-343-

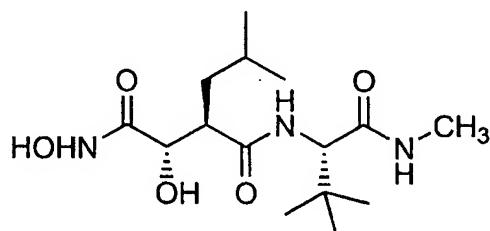
52. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

53. The method of Claim 1 wherein the matrix
10 metalloproteinase inhibitor is

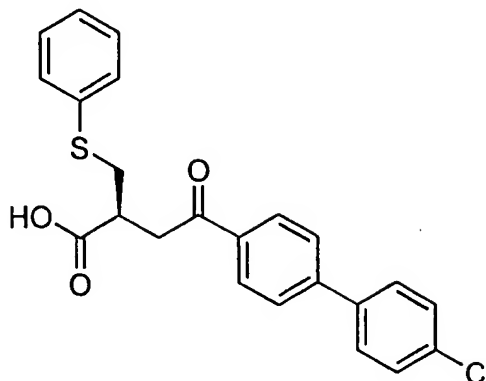


15

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-).

-349-

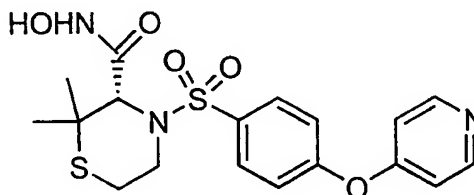
54. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5 Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid.

55. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

10



15 Agouron Pharmaceuticals AG-3340, N-hydroxy-
2,2-dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl]- 3-
thiomorpholinecarboxamide.

56. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is CollaGenex
Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-
20 dedimethylaminotetracycline.

57. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-[1S- ((2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-L- leucyl)amino- 3- methylbutyl]imidazole.

5

58. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a
10 combination of radiation, a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor, and an antineoplastic agent, wherein said antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin,
15 Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen,
20 thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone, exemestane and eflornithine (DFMO).

25 59. The method of Claim 58 wherein the combination is administered in a sequential manner.

60. The method of Claim 58 wherein the combination is administered in a substantially simultaneous manner.

30

-351-

61. The method of Claim 58 wherein the antineoplastic agent is capecitabine.

62. The method of Claim 58 wherein the antineoplastic agent is carboplatin.

63. The method of Claim 58 wherein the antineoplastic agent is cisplatin.

64. The method of Claim 58 wherein the antineoplastic agent is Cell Pathways CP-461.

65. The method of Claim 58 wherein the antineoplastic agent is docetaxel.

66. The method of Claim 58 wherein the antineoplastic agent is doxorubicin.

67. The method of Claim 58 wherein the antineoplastic agent is etoposide.

68. The method of Claim 58 wherein the antineoplastic agent is fluoxymestrine.

69. The method of Claim 58 wherein the antineoplastic agent is gemcitabine.

70. The method of Claim 58 wherein the antineoplastic agent is goserelin.

71. The method of Claim 58 wherein the antineoplastic agent is irinotecan.

-353-

82. The method of Claim 58 wherein the antineoplastic agent is thiotepa.

83. The method of Claim 58 wherein the
5 antineoplastic agent is topotecan.

84. The method of Claim 58 wherein the antineoplastic agent is toremifene.

10 85. The method of Claim 58 wherein the antineoplastic agent is vinorelbine.

86. The method of Claim 58 wherein the antineoplastic agent is vinblastine.
15

87. The method of Claim 58 wherein the antineoplastic agent is vincristine.

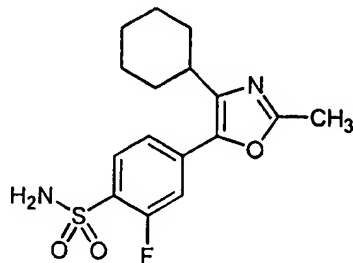
88. The method of Claim 58 wherein the
20 antineoplastic agent is selenium (selenomethionine).

89. The method of Claim 58 wherein the antineoplastic agent is sulindac sulfone.

25 90. The method of Claim 58 wherein the antineoplastic agent is eflornithine (DFMO).

91. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

5 1)



JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide,

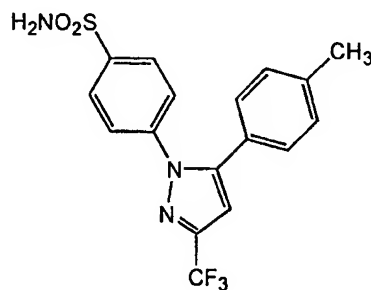
2)

10 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

3)

2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

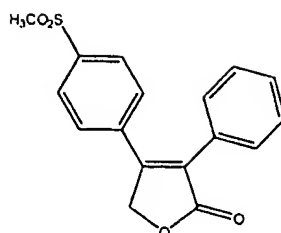
15 4)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

-355-

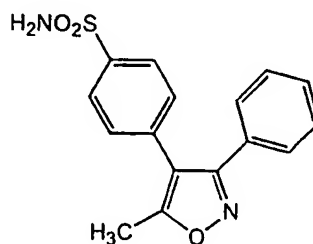
5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

5

6)



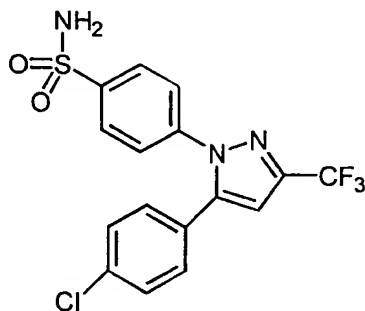
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

7)

N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

10

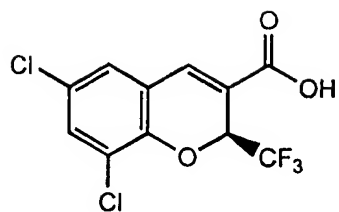
8)



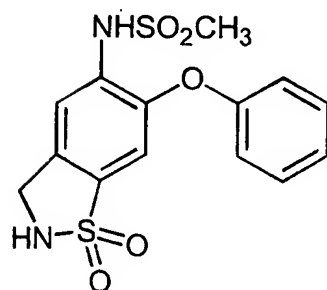
4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

-356-

9)

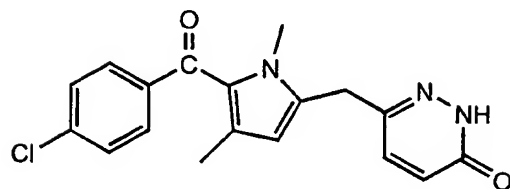


10)



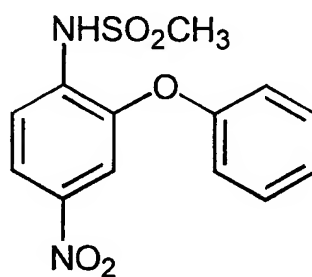
5

11)



6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

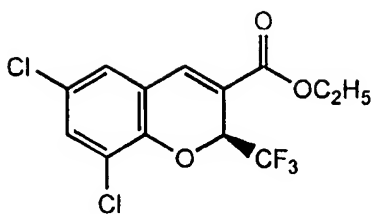
12)



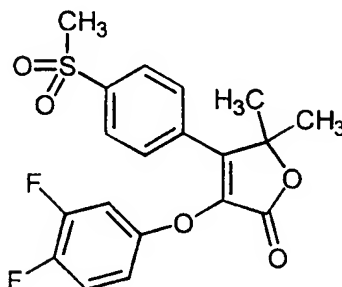
10

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)



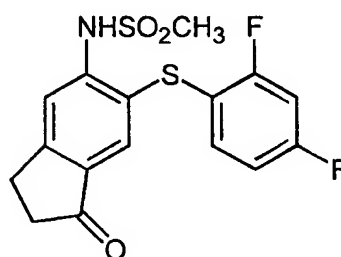
14)



5

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

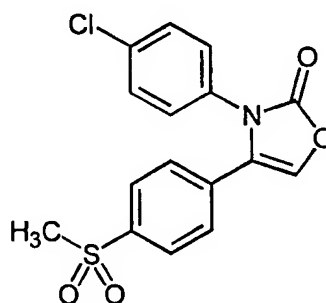
15)



10

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

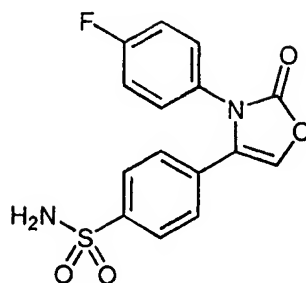
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

-358-

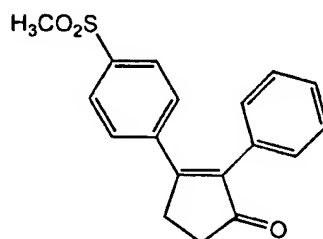
17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

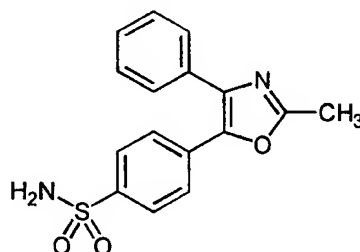
5

18)



3-[4-(methanesulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

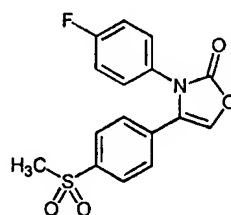
19)



10

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

20)

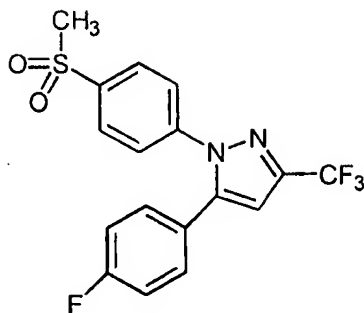


15

3-(4-fluorophenyl)-4-[4-(methanesulfonyl)phenyl]-2(3H)-oxazolone,

-359-

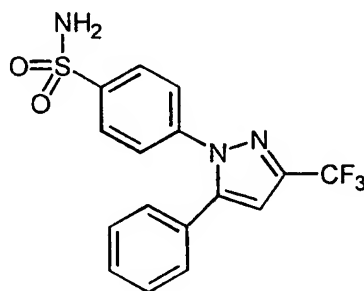
21)



5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-
1H-pyrazole,

5

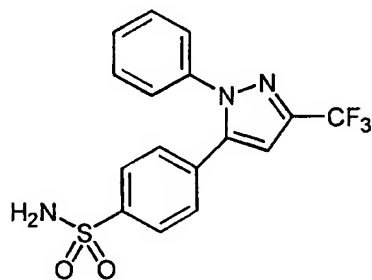
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

10

23)

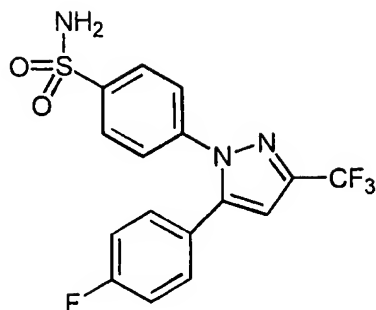


4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

15

-360-

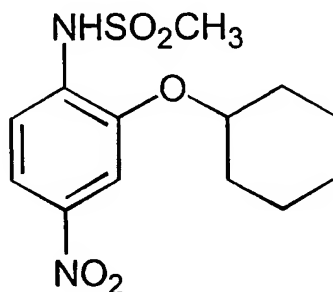
24)



4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

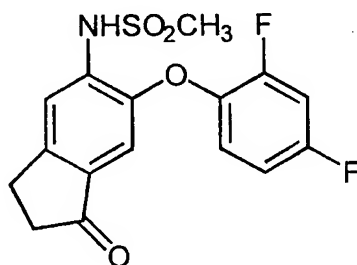
5

25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

26)

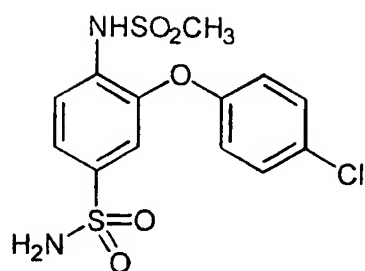


10

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

-361-

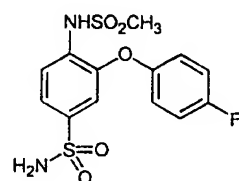
27)



3-(4-chlorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide,

5

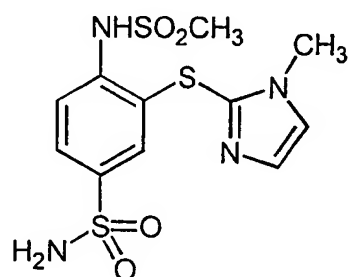
28)



3-(4-fluorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide,

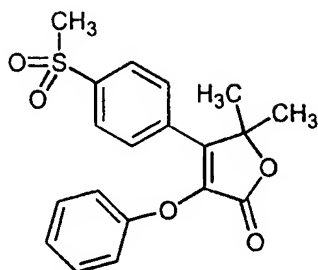
10

29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4
[(methylsulfonyl) amino]benzenesulfonamide,

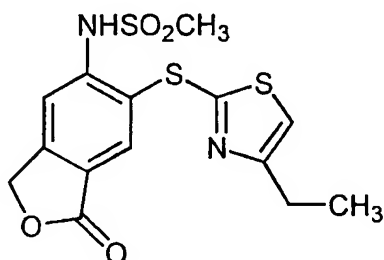
30)



5

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone,

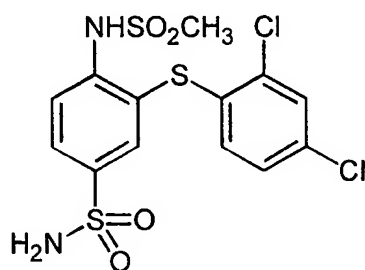
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

10

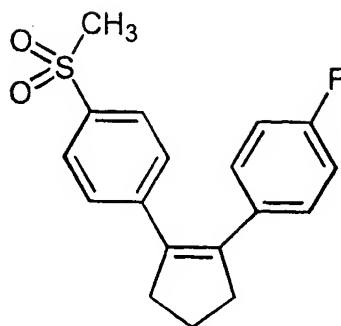
32)



3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide,

-363-

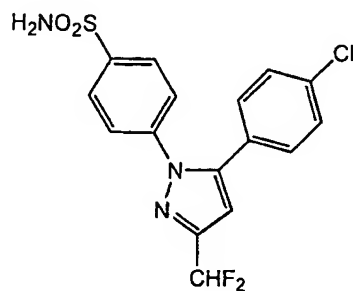
33)



1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene,

5

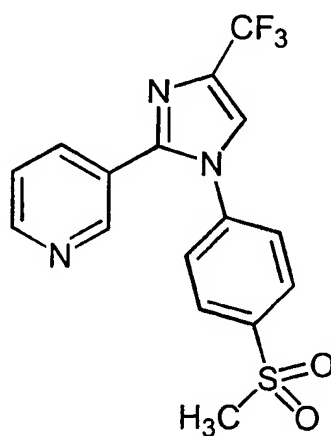
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

10

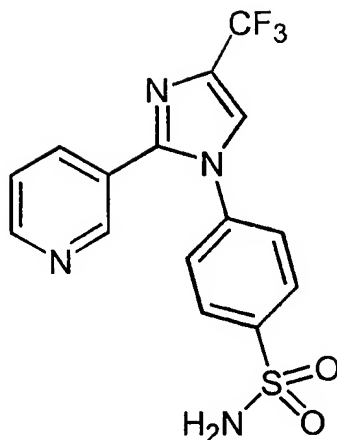
35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

-364-

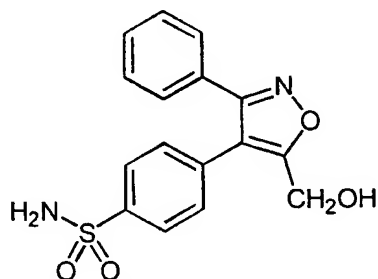
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

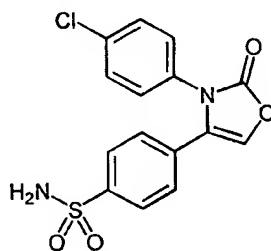
5

37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

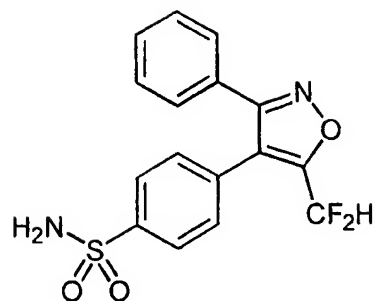
38)



10

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

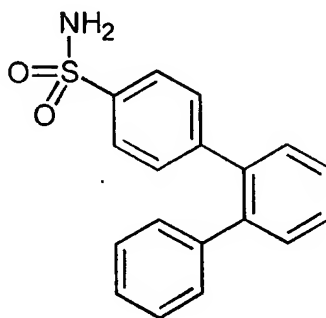
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

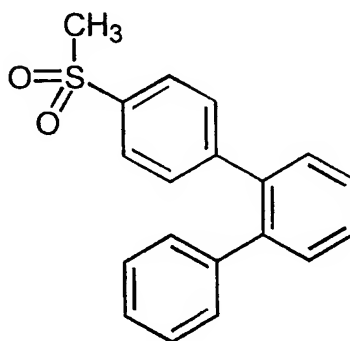
5

40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

41)

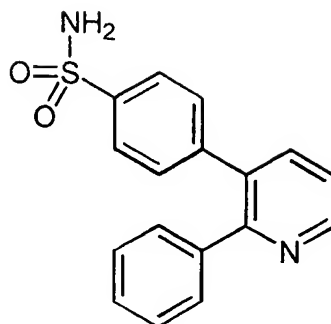


10

4-(methylsulfonyl)-1,1',2',1''-terphenyl,

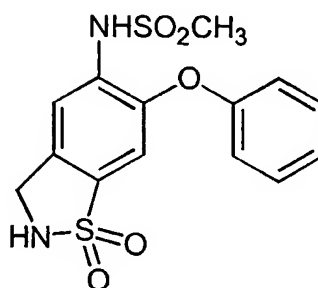
-366-

42)



4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

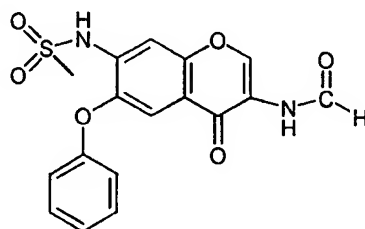
43)



5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

44)

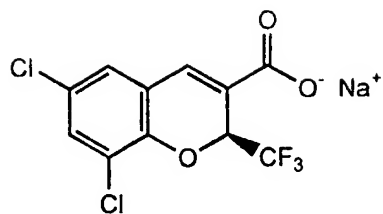


10

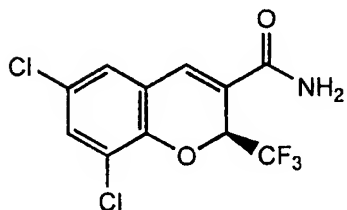
N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

-367-

45)

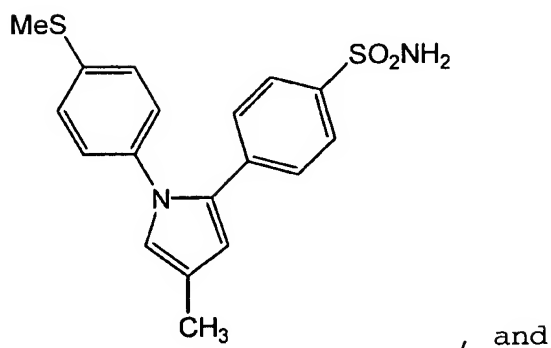


46)

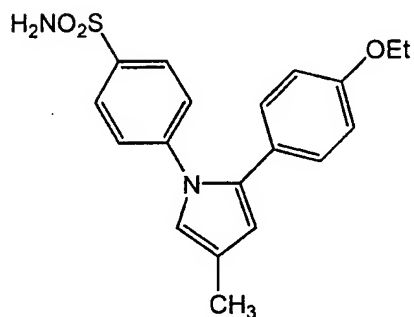


5

47)



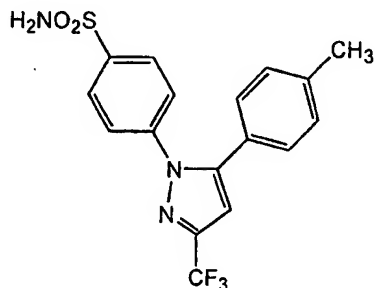
48)



92. The method of Claim 58 wherein the
 10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

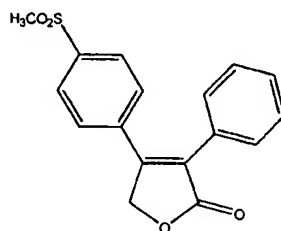
93. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

94. The method of Claim 58 wherein the
5 cyclooxygenase-2 inhibitor is



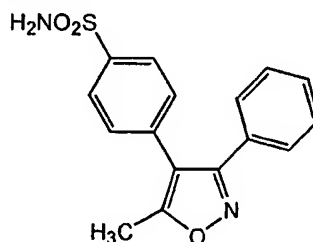
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

95. The method of Claim 58 wherein the
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

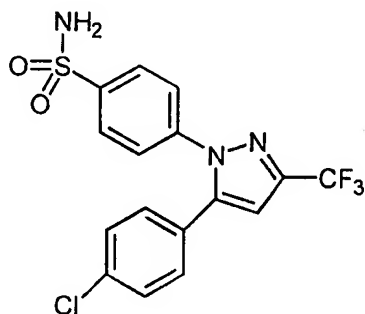
15 96. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is



4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

97. The method of Claim 58 wherein the cyclooxygenase-2 inhibitor is N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl)sulfonyl]propanamide.

98. The method of Claim 58 wherein the
5 cyclooxygenase-2 inhibitor is



4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide.

99. The method of Claim 58 wherein the neoplasia
10 is selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

100. The method of Claim 58 wherein the neoplasia
is selected from the group consisting of acral
15 lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenocarcinoma, adenosquamous carcinoma, astrocytic tumors, Bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma,
20 carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epithelioid,
25 Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma,

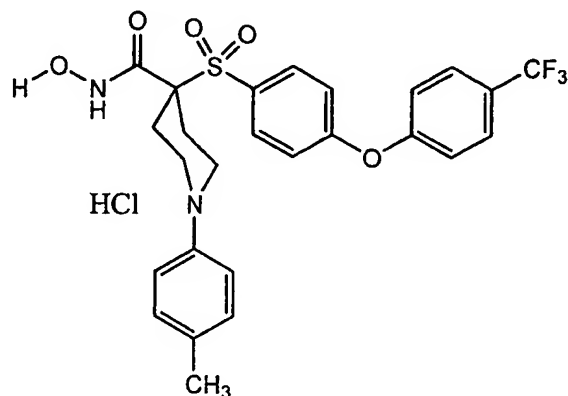
-370-

glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, 5 invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, 10 neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal 15 cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, 20 undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

-371-

101. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

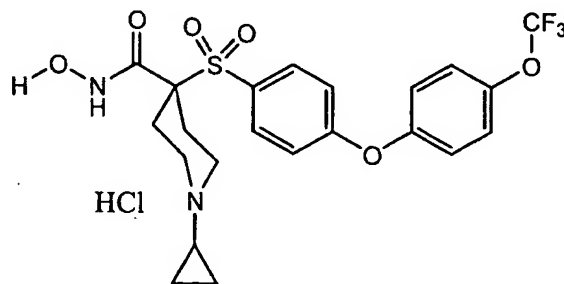
5 1)



N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

10

2)

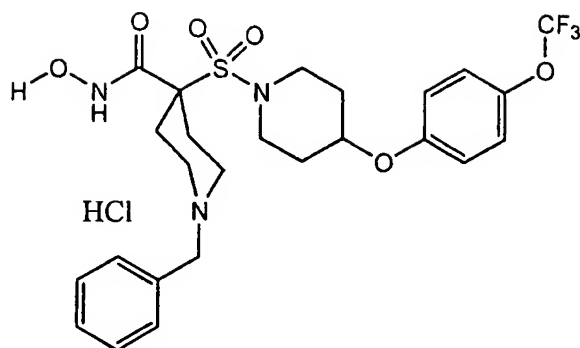


1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

15

-372-

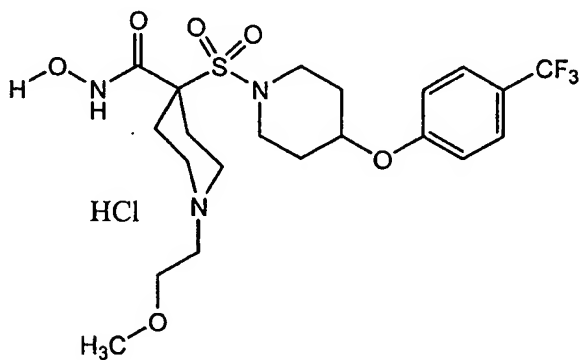
3)



5

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

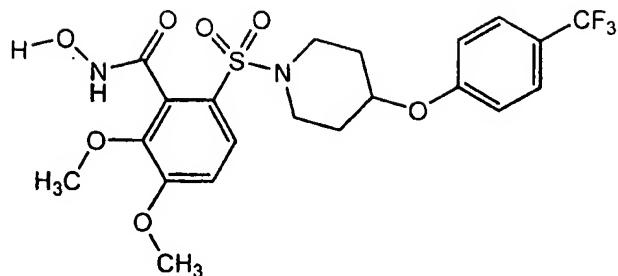
4)



10

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

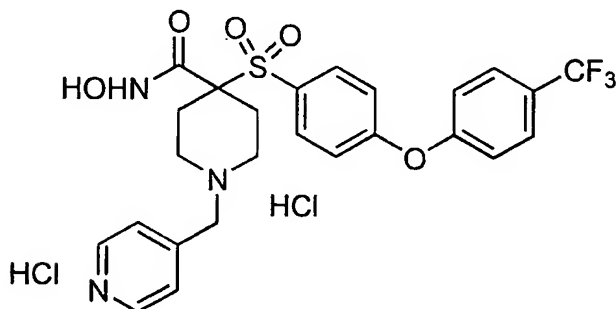
5)



5

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

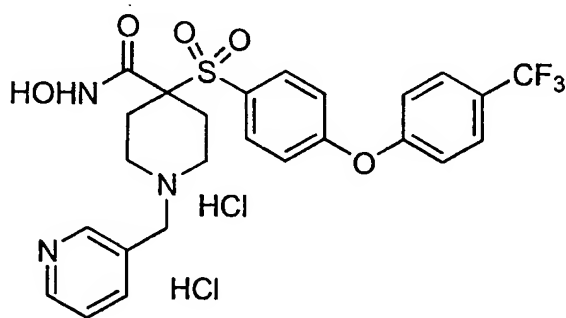
6)



10

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

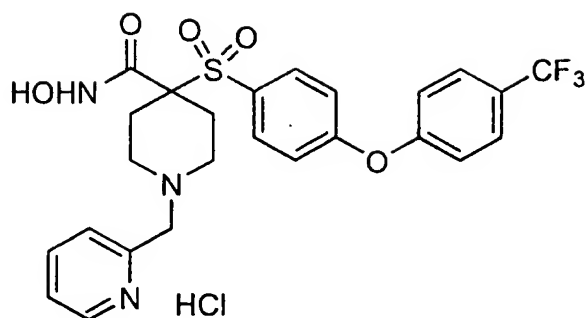
7)



15

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

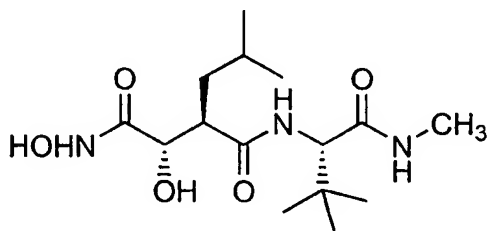
8)



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

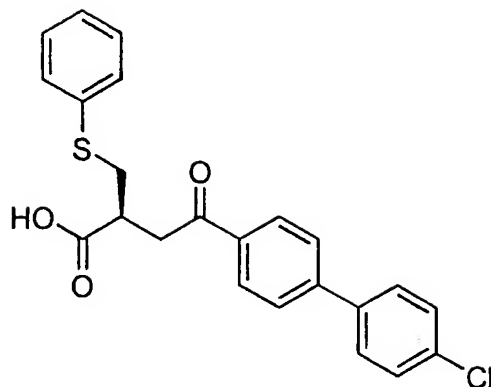


10

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-,

-375-

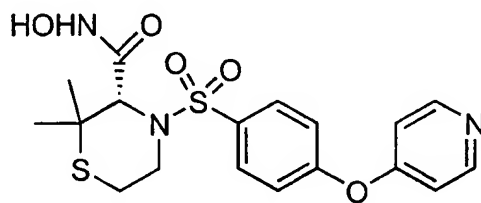
10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid,

5

11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2
dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl] 3-
thiomorpholinecarboxamide,

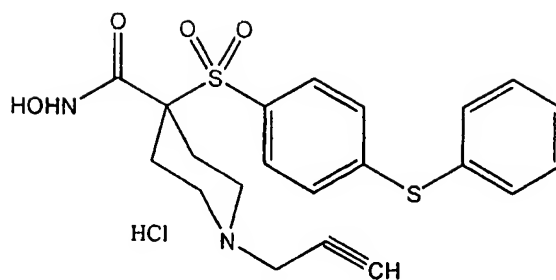
10

12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
6-demethyl-6-deoxy-4-
dedimethylaminotetracycline,

15

13) Chiroscience D-2163, 2- [1S- ((2R,S)-
acetylmercapto- 5- phthalimido]pentanoyl- L-
leucyl)amino- 3- methylbutyl]imidazole,

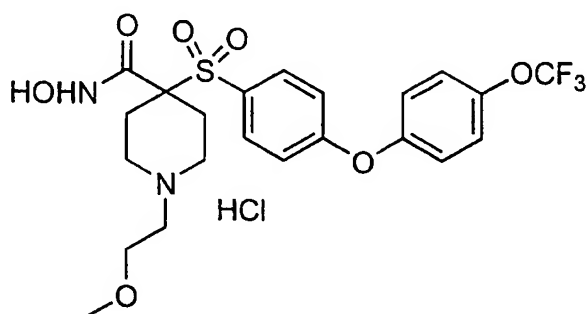
14)



N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide
monohydrochloride,

5

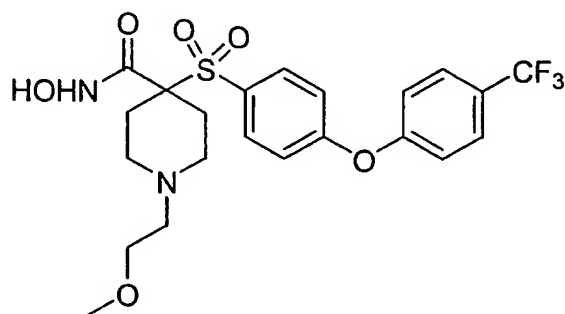
15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride,

10

16)

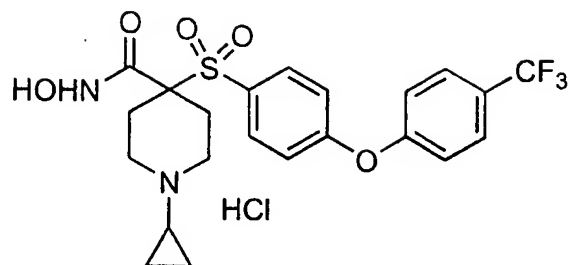


N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide,

15

-377-

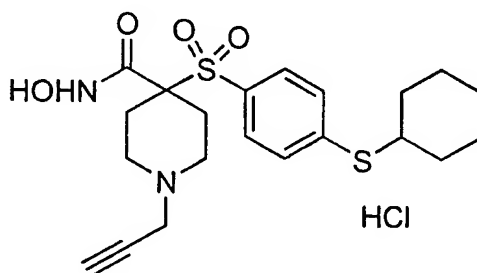
17)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

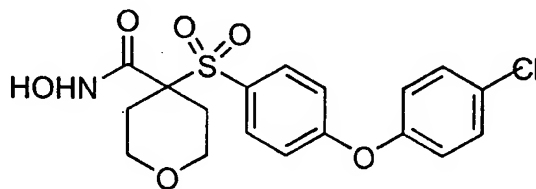
18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

10

19)

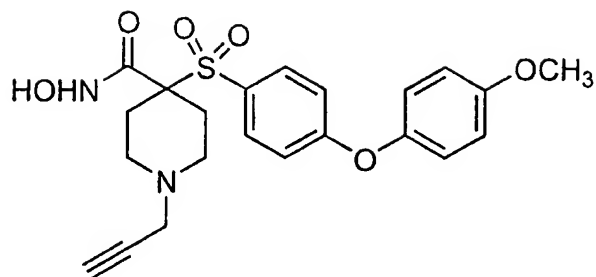


4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

15

-373-

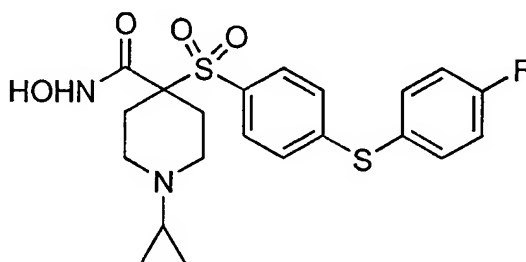
20)



5

N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

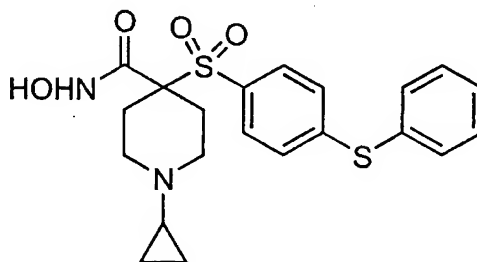
21)



10

1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

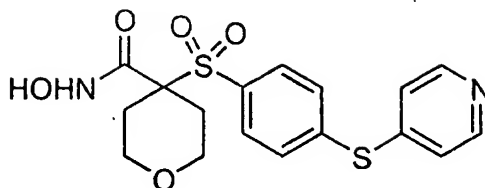
22)



15

1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

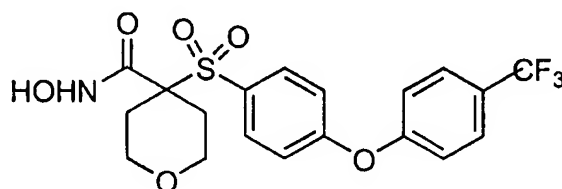
23)



tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

5

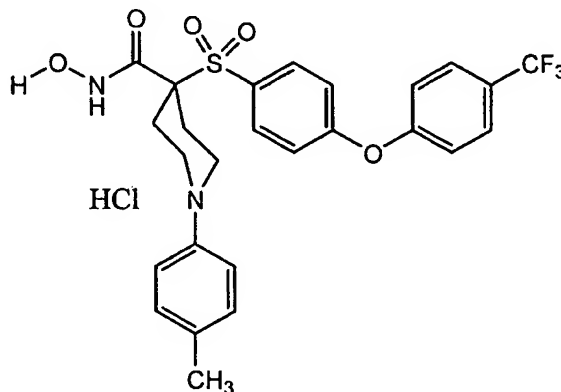
24)



tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide.

10

102. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

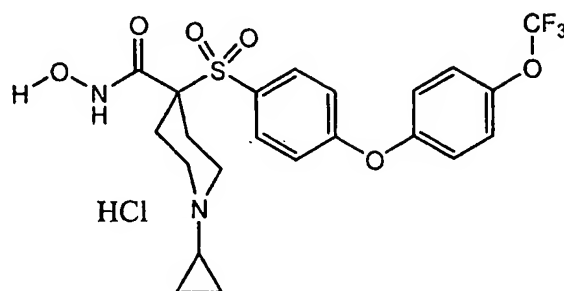


N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

15

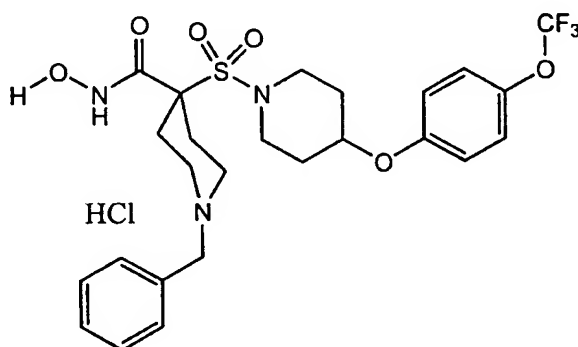
-380-

103. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



5 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

104. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

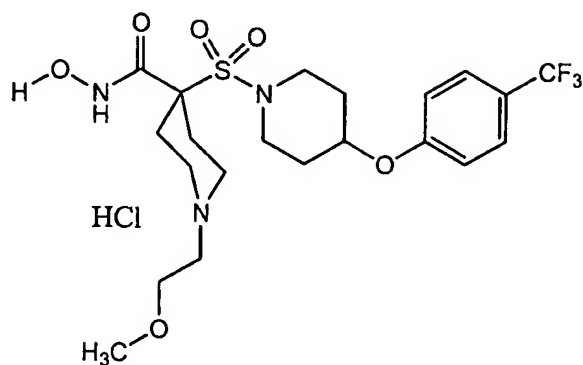


10

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

-381-

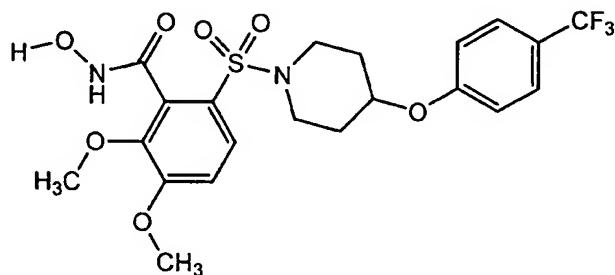
105. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-piperidinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

106. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

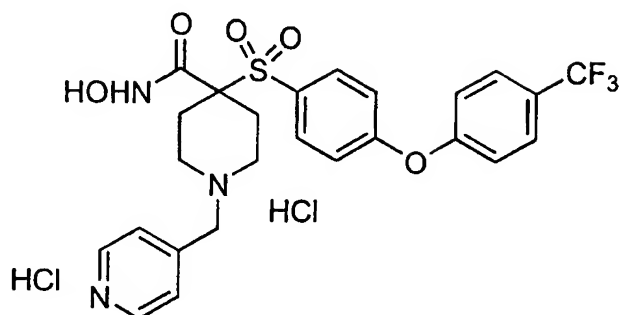
10



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

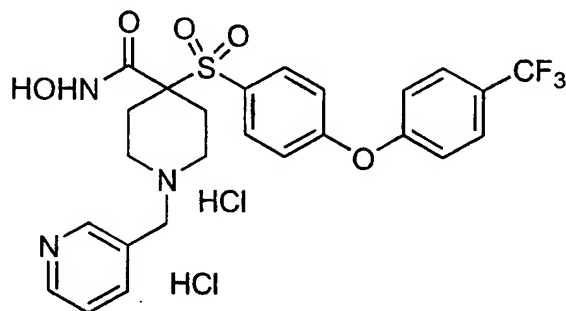
-332-

107. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

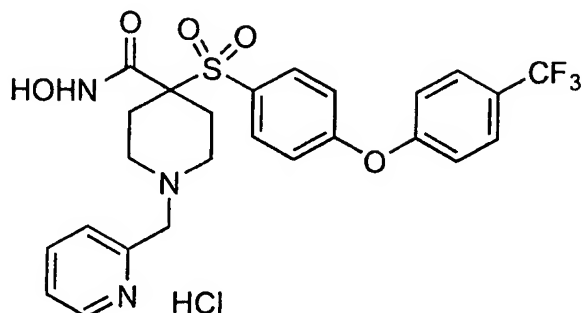
108. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



15 N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

-383-

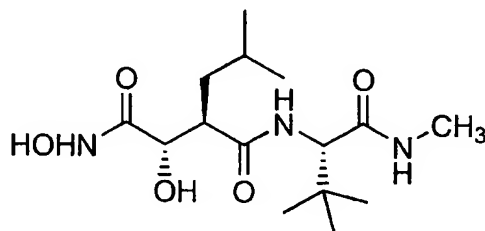
109. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

110. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is

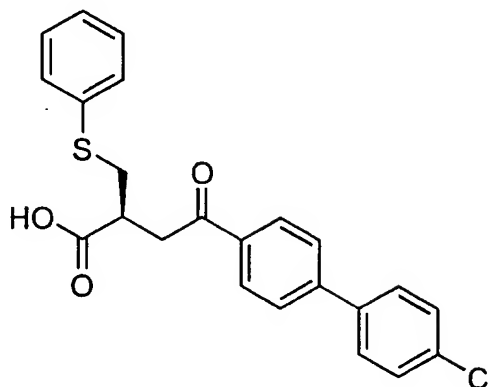


15

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-).

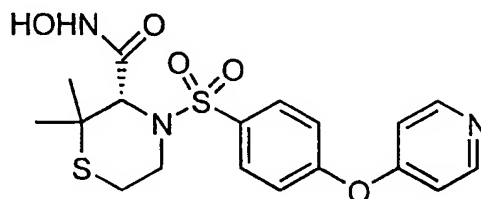
-384-

111. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



5 Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid.

112. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is



10 Agouron Pharmaceuticals AG-3340, N-hydroxy-
2,2-dimethyl-4-[[4-(4-
15 pyridinyloxy)phenyl]sulfonyl]- 3-
thiomorpholinecarboxamide.

113. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is CollaGenex
Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-
20 dedimethylaminotetracycline.

114. The method of Claim 58 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-

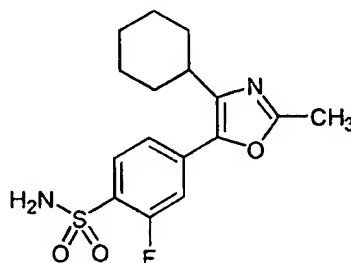
-385-

[1S- ([[(2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-
L- leucyl)amino- 3- methylbutyl]imidazole.

115. A combination comprising a cyclooxygenase-2
5 inhibitor, a matrix metalloproteinase inhibitor, and an
antineoplastic agent, wherein said antineoplastic agent
is selected from the group consisting of anastrozole,
calcium carbonate, capecitabine, carboplatin, cisplatin,
Cell Pathways CP-461, docetaxel, doxorubicin, etoposide,
10 fluorouracil (5-FU), fluoxymestrine, gemcitabine,
goserelin, irinotecan, ketoconazole, letrozol,
leucovorin, levamisole, megestrol, mitoxantrone,
paclitaxel, raloxifene, retinoic acid, tamoxifen,
thiotepa, topotecan, toremifene, vinorelbine,
15 vinblastine, vincristine, selenium (selenomethionine),
ursodeoxycholic acid, sulindac sulfone, exemestane and
eflornithine (DFMO).

116. The combination of Claim 115 wherein the
20 cyclooxygenase-2 inhibitor is selected from compounds,
and their pharmaceutically acceptable salts thereof, of
the group consisting of:

1)



25 JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-
2-fluorobenzenesulfonamide,

2)

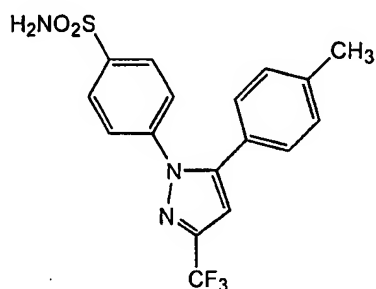
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine,

3)

5

2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one,

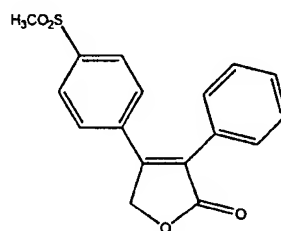
4)



10

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide,

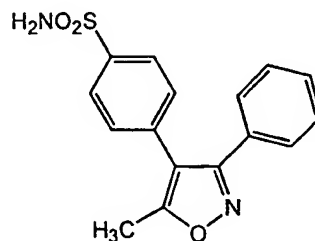
5)



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone,

15

6)

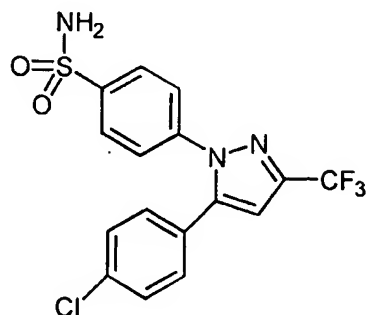


4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide,

-87-

- 7) N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide,

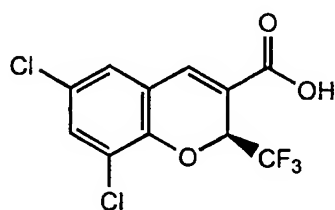
8)



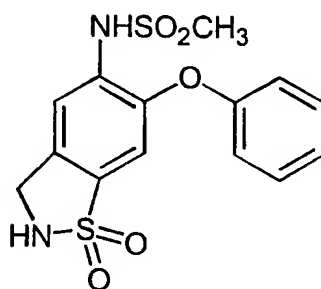
5

- 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide,

9)

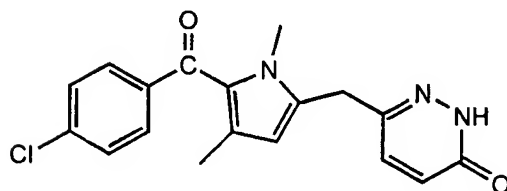


10)



10

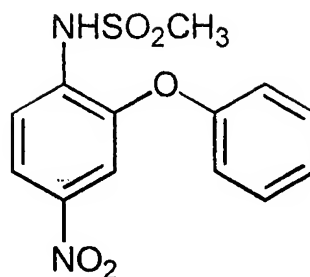
11)



- 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,

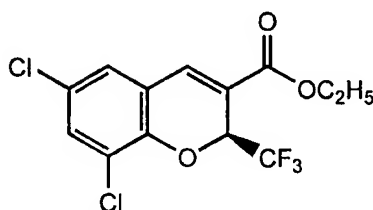
-388-

12)



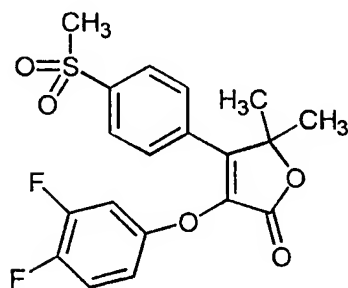
N-(4-nitro-2-phenoxyphenyl)methanesulfonamide,

13)



5

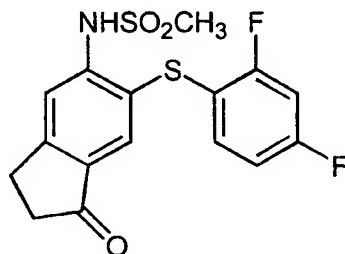
14)



3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone,

10

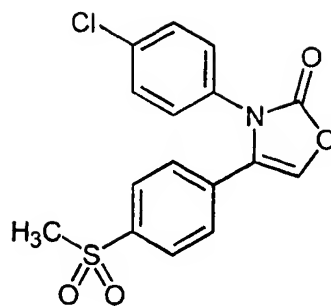
15)



N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

-389-

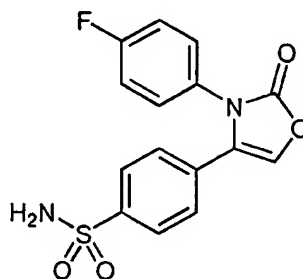
16)



3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

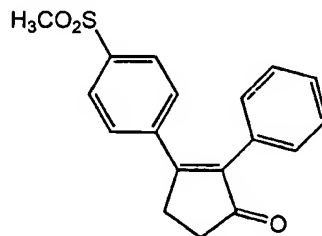
5

17)



4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

18)

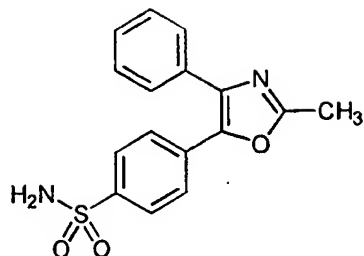


10

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one,

-390-

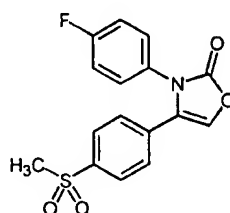
19)



4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide,

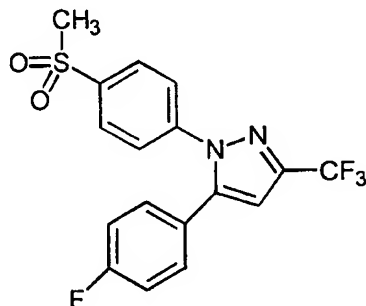
5

20)



3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone,

21)

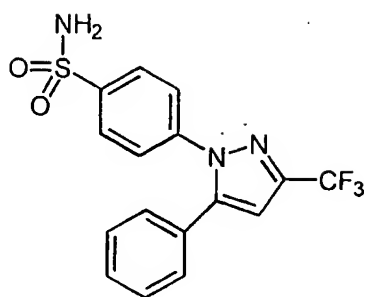


10

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole,

-391-

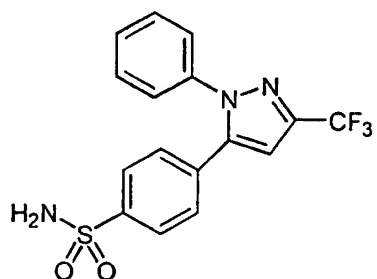
22)



4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

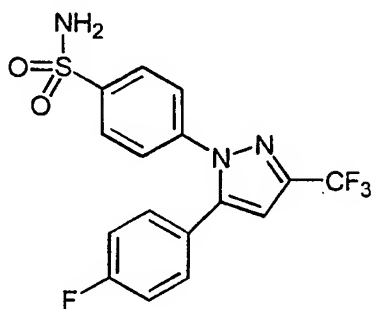
5

23)



4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide,

24)

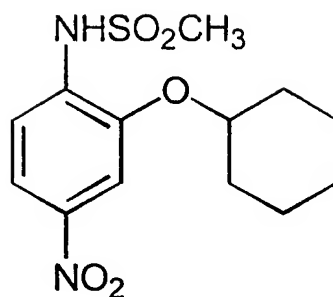


10

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

-392-

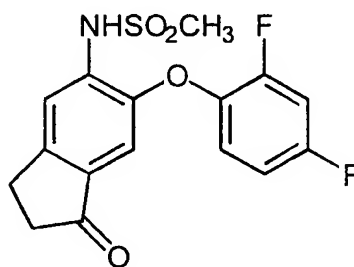
25)



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide,

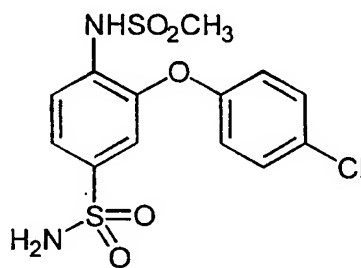
5

26)



N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide,

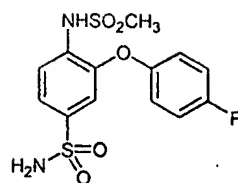
27)



10

3-(4-chlorophenoxy)-4-[(methanesulfonyl)amino]benzenesulfonamide,

28)

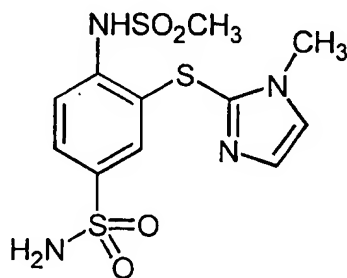


3-(4-fluorophenoxy)-4-

[(methylsulfonyl)amino]benzenesulfonamide,

5

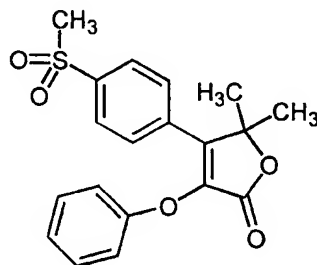
29)



3-[(1-methyl-1H-imidazol-2-yl)thio]-4

[(methylsulfonyl)amino]benzenesulfonamide,

30)

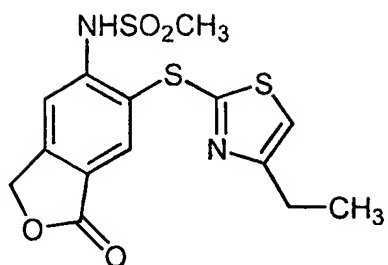


10

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-
phenoxy-2(5H)-furanone,

-394-

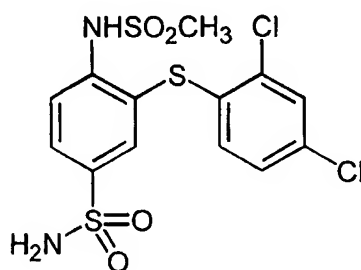
31)



N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide,

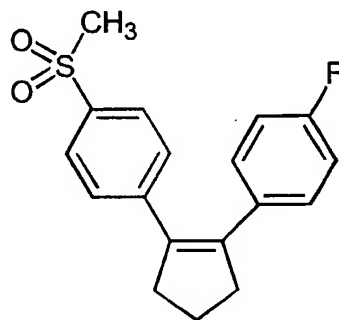
5

32)



3-[(2,4-dichlorophenyl)thio]-4-[(methanesulfonyl)amino]benzenesulfonamide,

33)

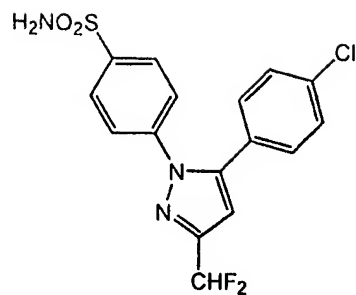


10

1-fluoro-4-[2-[4-(methanesulfonyl)phenyl]cyclopenten-1-yl]benzene,

-395-

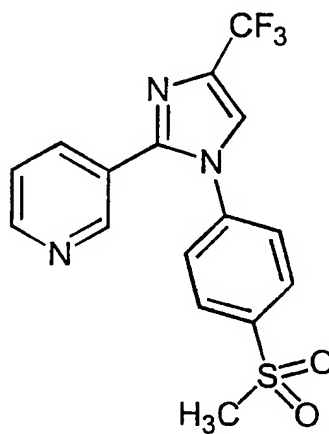
34)



4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide,

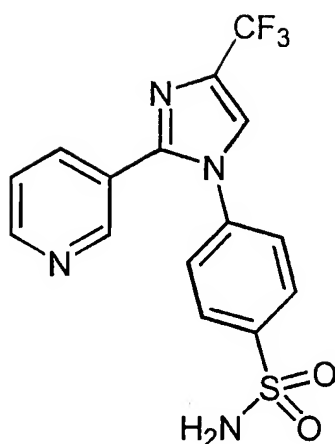
5

35)



3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine,

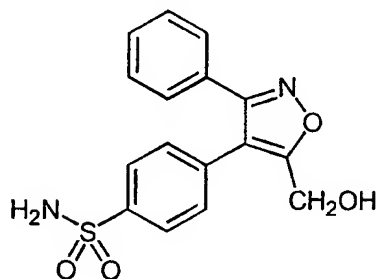
36)



4-[2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide,

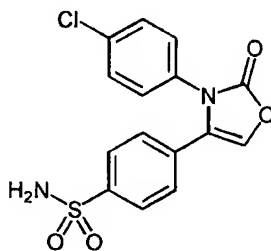
5

37)



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

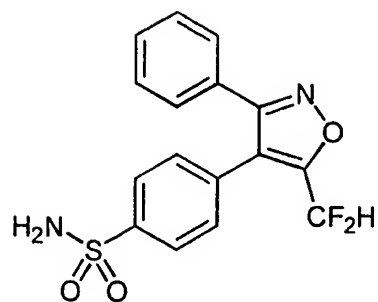
38)



4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide,

-397-

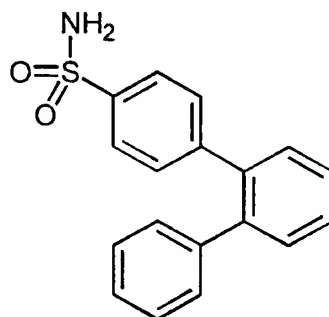
39)



4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide,

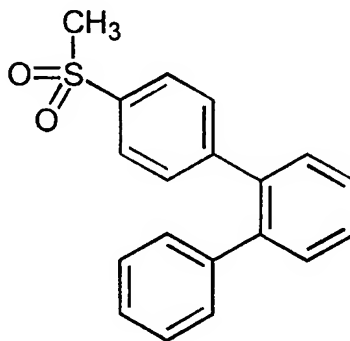
5

40)



[1,1':2',1''-terphenyl]-4-sulfonamide,

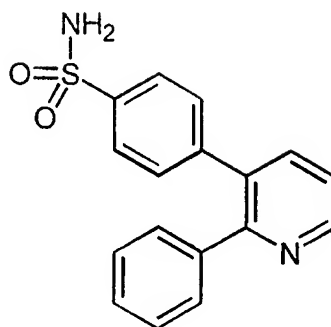
41)



10

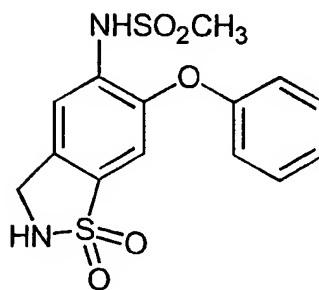
4-(methylsulfonyl)-1,1',2',1''-terphenyl,

42)



4-(2-phenyl-3-pyridinyl)benzenesulfonamide,

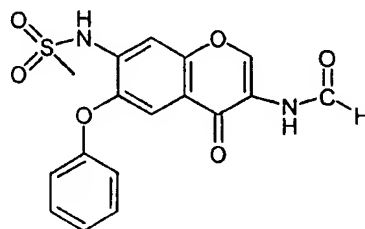
43)



5

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide, and

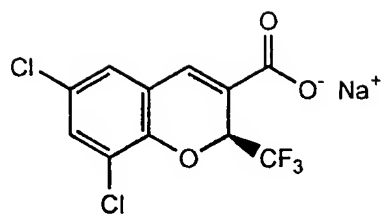
44)



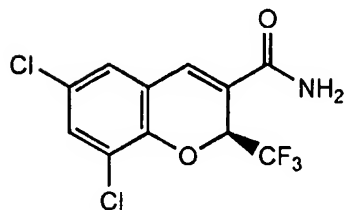
10

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide,

45)

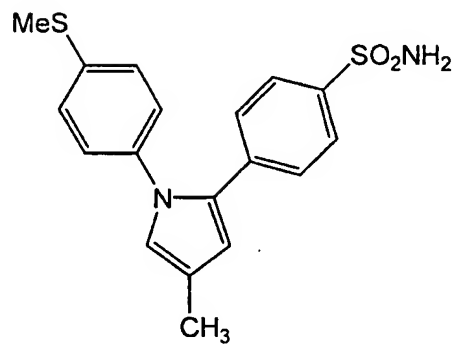


46)



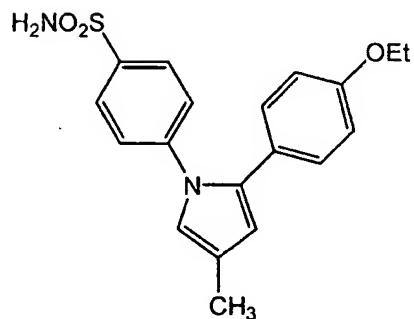
5

47)



, and

48)

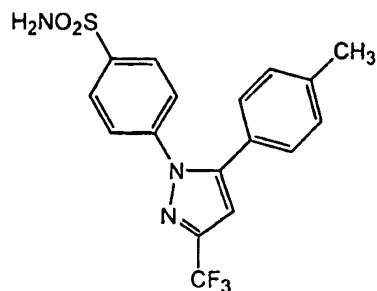


117. The combination of Claim 115 wherein the
 10 cyclooxygenase-2 inhibitor is 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)pyridine.

400-

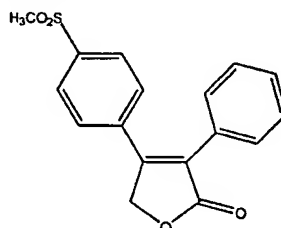
118. The combination of Claim 115 wherein the cyclooxygenase-2 inhibitor is 2-(3,5-difluorophenyl)-3-4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one.

119. The combination of Claim 115 wherein the
5 cyclooxygenase-2 inhibitor is



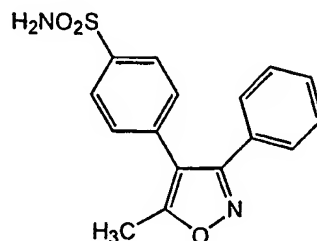
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide.

120. The combination of Claim 115 wherein the
10 cyclooxygenase-2 inhibitor is



rofecoxib, 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone.

121. The combination of Claim 115 wherein the
15 cyclooxygenase-2 inhibitor is



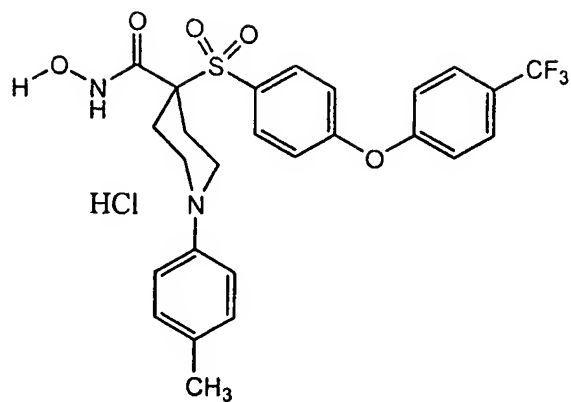
4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide.

- 402 -

- glucagonoma, hemangiblastomas, hemangioendothelioma,
hemangiomas, hepatic adenoma, hepatic adenomatosis,
hepatocellular carcinoma, insulinoma, intraepithelial
neoplasia, interepithelial squamous cell neoplasia,
5 invasive squamous cell carcinoma, large cell carcinoma,
leiomyosarcoma, lentigo maligna melanomas, malignant
melanoma, malignant mesothelial tumors, medulloblastoma,
medulloepithelioma, melanoma, meningeal, mesothelial,
metastatic carcinoma, mucoepidermoid carcinoma,
10 neuroblastoma, neuroepithelial adenocarcinoma nodular
melanoma, oat cell carcinoma, oligodendroglial,
osteosarcoma, pancreatic polypeptide, papillary serous
adenocarcinoma, pineal cell, pituitary tumors,
plasmacytoma, pseudosarcoma, pulmonary blastoma, renal
15 cell carcinoma, retinoblastoma, rhabdomyosarcoma,
sarcoma, serous carcinoma, small cell carcinoma, soft
tissue carcinomas, somatostatin-secreting tumor,
squamous carcinoma, squamous cell carcinoma,
submesothelial, superficial spreading melanoma,
20 undifferentiated carcinoma, uveal melanoma, verrucous
carcinoma, vipoma, well differentiated carcinoma, and
Wilm's tumor.

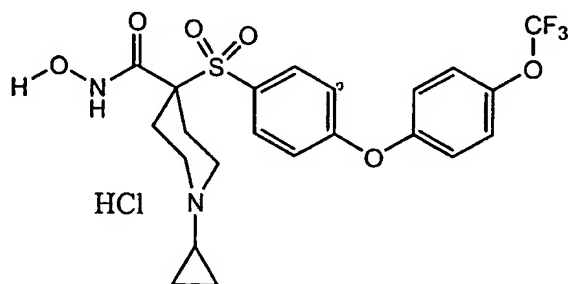
126. The combination of Claim 115 wherein the
25 matrix metalloproteinase inhibitor is selected from
compounds, and their pharmaceutically acceptable salts
thereof, of the group consisting of:

1)



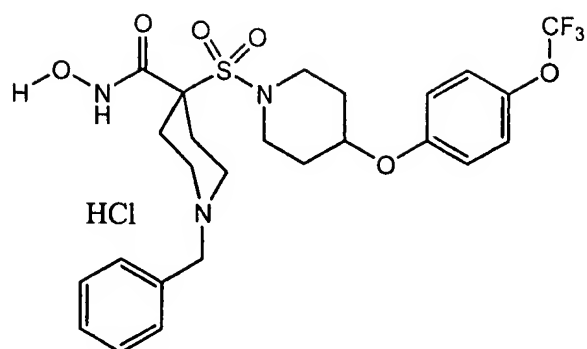
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

2)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

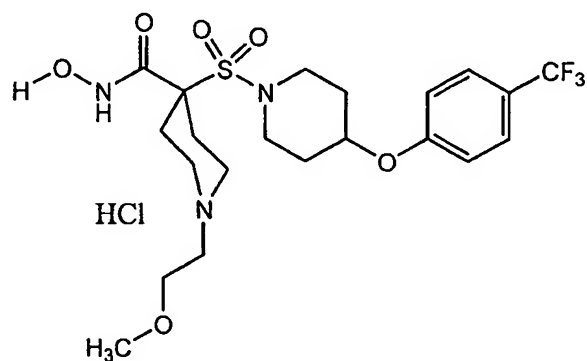
3)



N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

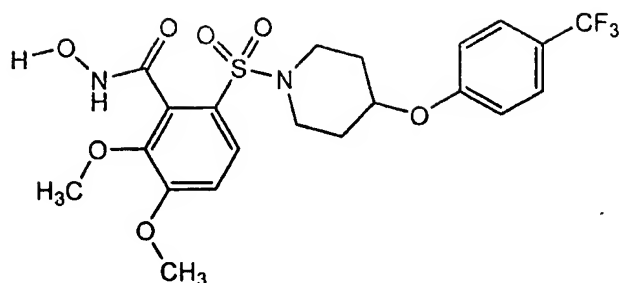
4)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

10

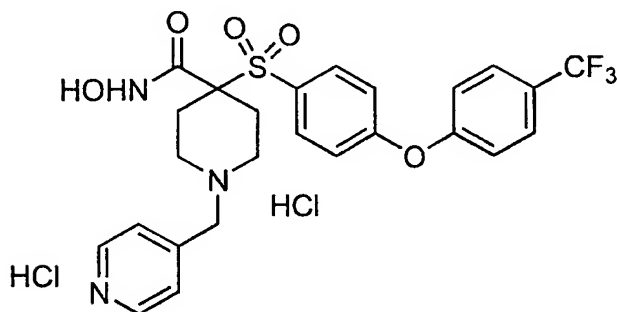
5)



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidiny]sulfonyl]benzamide,

5

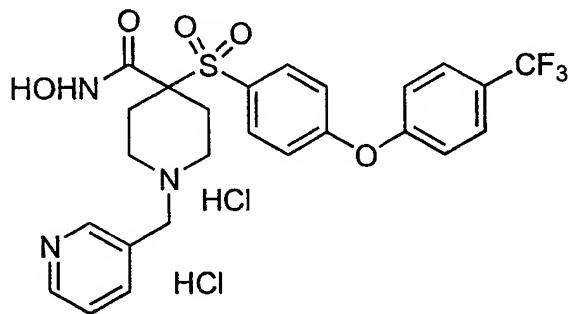
6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

10

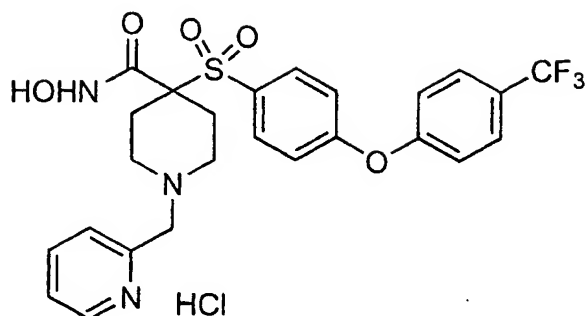
7)



N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

15

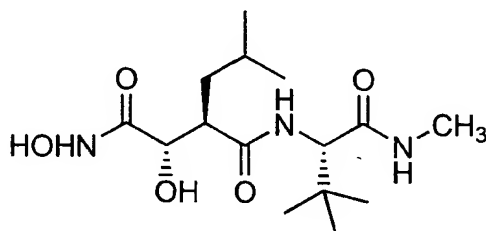
8)



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

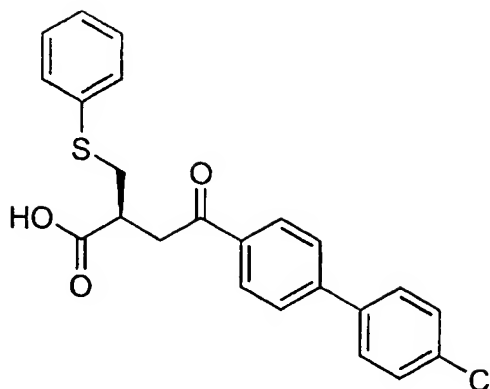


10

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-,

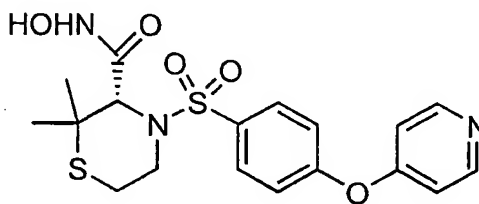
4.07-

10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid,

11)



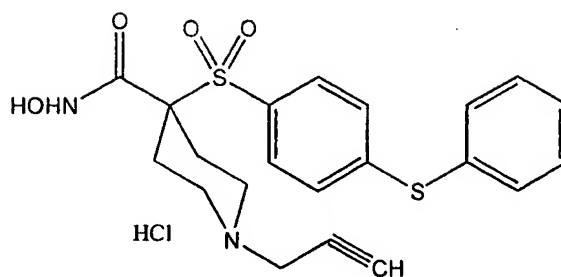
Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2
dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl] 3-
thiomorpholinecarboxamide,

12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
6-demethyl-6-deoxy-4-

dedimethylaminotetracycline,

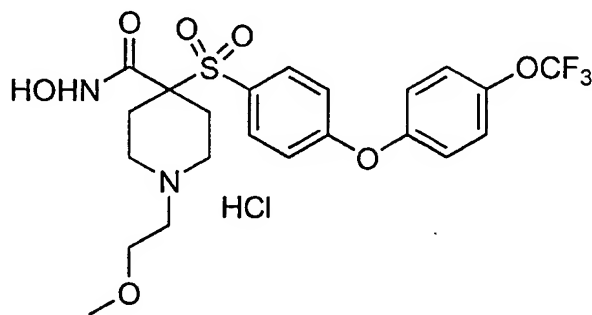
13) Chiroscience D-2163, 2- [1S- ((2R,S)-
acetylmercapto- 5- phthalimido]pentanoyl- L-
leucyl)amino- 3- methylbutyl]imidazole,

14)



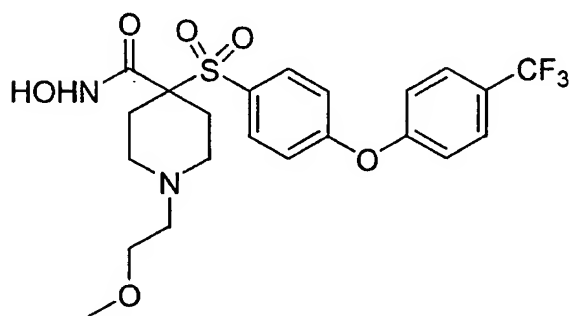
N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide
monohydrochloride,

15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride,

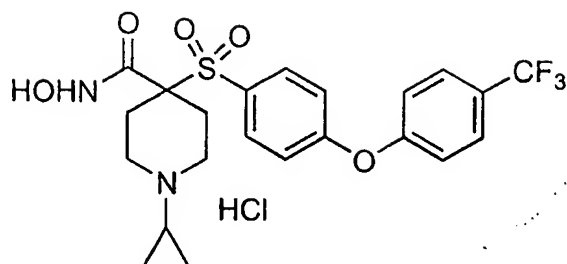
16)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide,

-409-

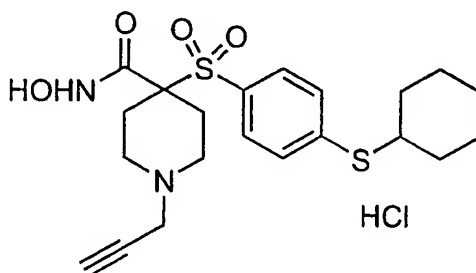
17)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

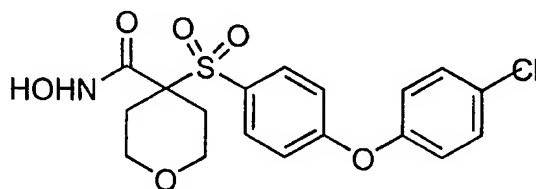
18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

10

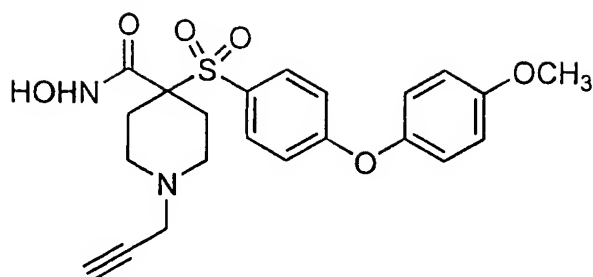
19)



4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

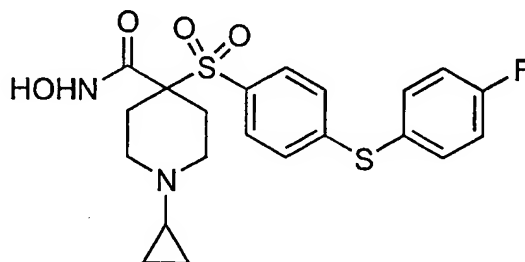
15

20)



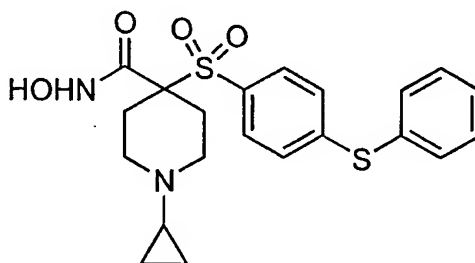
N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

21)



1-cyclopropyl-4-[[4-(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

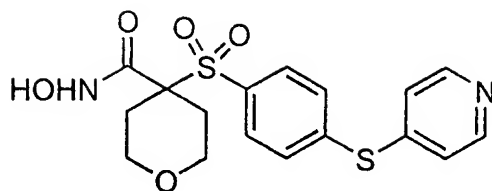
22)



1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

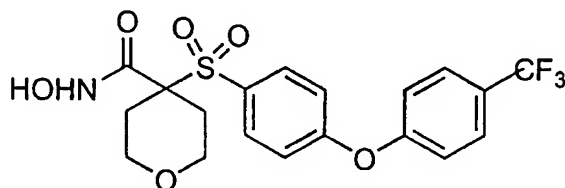
-411-

23)



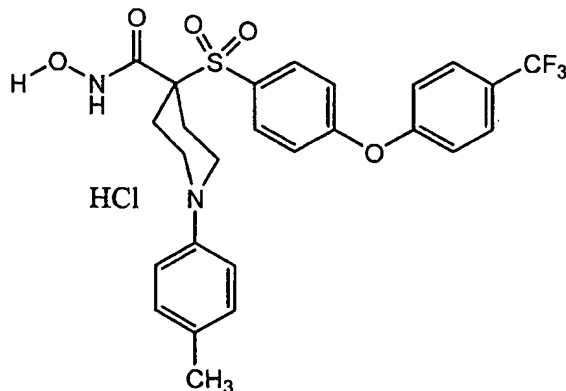
tetrahydro-N-hydroxy-4-[[4-(4-
pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-
carboxamide, and

24)



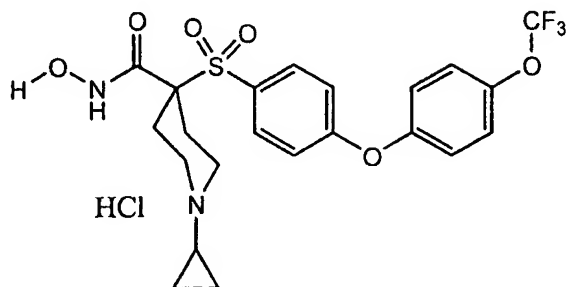
tetrahydro-N-hydroxy-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-
pyran-4-carboxamide.

127. The combination of Claim 115 wherein the
matrix metalloproteinase inhibitor is



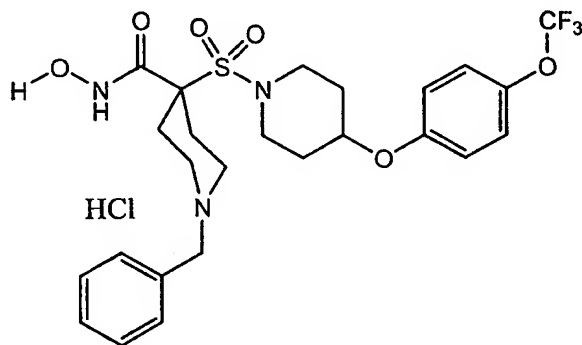
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride.

128. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



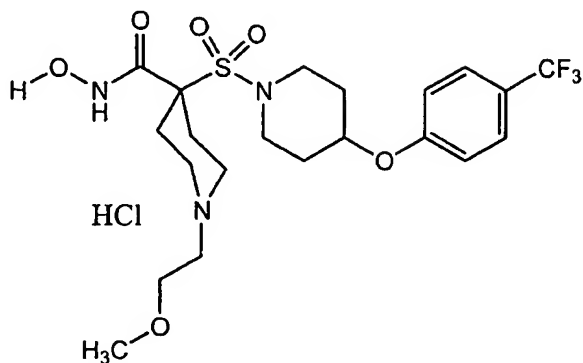
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

129. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

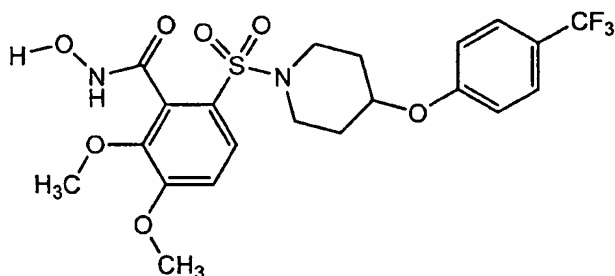
130. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-piperidinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

131. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

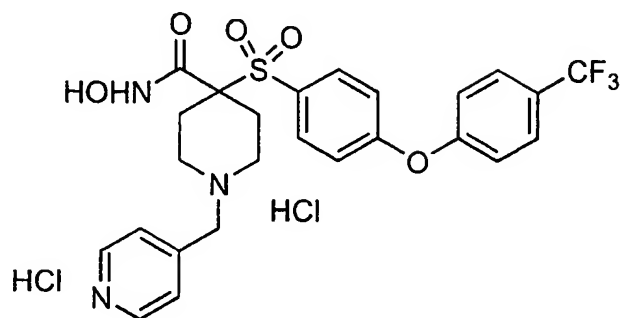
10



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

-14-

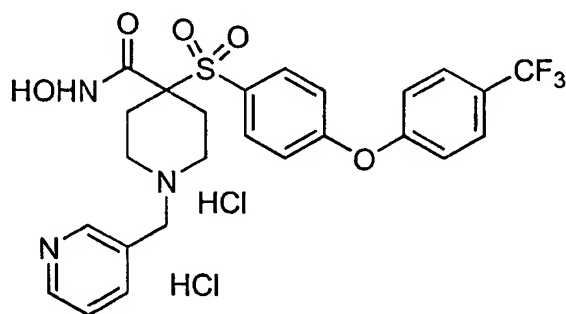
132. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

133. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is

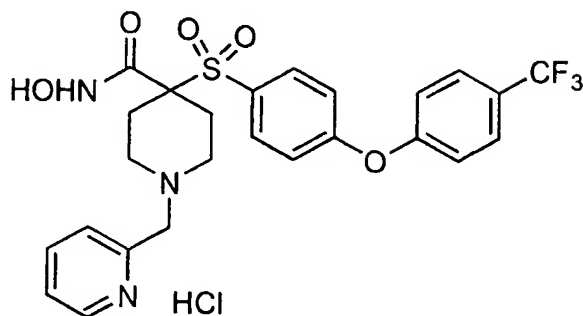
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15

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

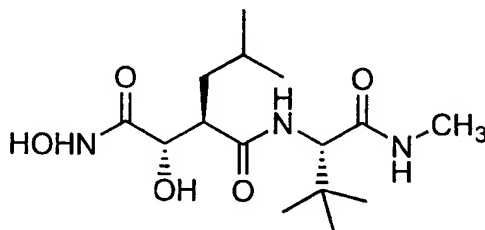
134. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[(4-(trifluoromethyl)phenoxy]phenyl)sulfonyl]-4-piperidinecarboxamide monohydrochloride.

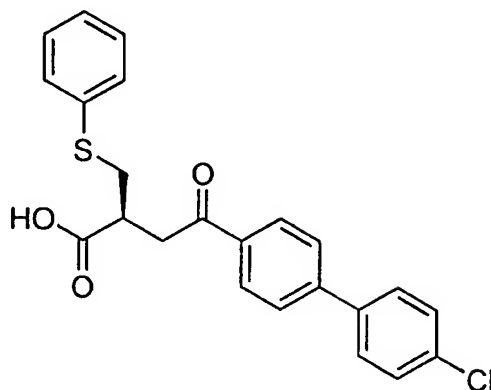
135. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



15

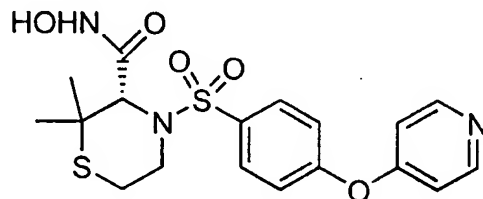
British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-).

136. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



5 Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid.

137. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is



15 Agouron Pharmaceuticals AG-3340, N-hydroxy-
2,2-dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl]- 3-
thiomorpholinecarboxamide.

138. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is CollaGenex
Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-
20 dedimethylaminotetracycline.

139. The combination of Claim 115 wherein the matrix metalloproteinase inhibitor is Chiroscience D-

2163, 2- [1S- ([(2R,S)- acetylmercapto- 5-
phthalimidol]pentanoyl- L- leucyl)amino- 3-
methylbutyl]imidazole.

5 140. The method of Claim 1 wherein the
antineoplastic agent is anastrozole.

141. The method of Claim 1 wherein the
antineoplastic agent is calcium carbonate.

10

142. The method of claim 1 wherein the
antineoplastic agent is exemestane.

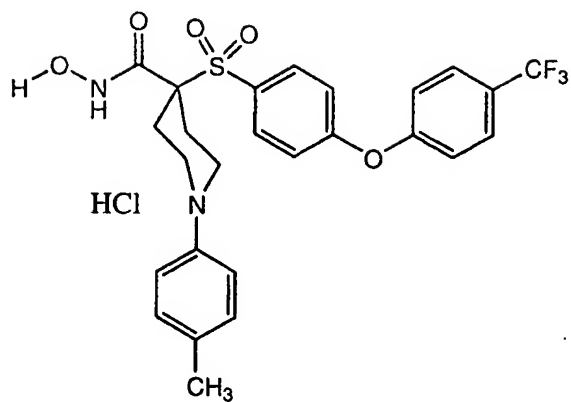
143. The method of Claim 58 wherein the combination
15 is administered in a sequential manner.

144. The method of Claim 58 wherein the combination
is administered in a substantially simultaneous manner.

20 145. The method of claim 1 wherein the
antineoplastic agent is exemestane.

146. A method for treating or preventing a
neoplasia disorder in a mammal in need of such treatment
25 or prevention, which method comprises administering to
said mammal a therapeutically-effective amount of a
combination of a cyclooxygenase-2 inhibitor and a matrix
metalloproteinase inhibitor, wherein said matrix
metalloproteinase inhibitor is selected from compounds,
30 and their pharmaceutically acceptable salts thereof, of
the group consisting of:

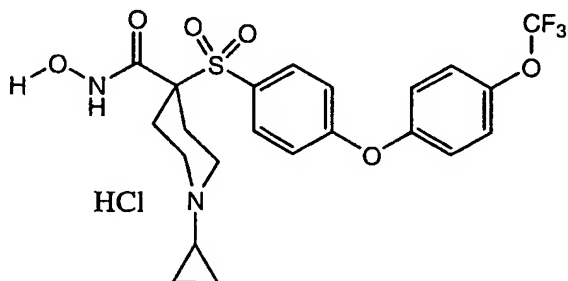
1)



5

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

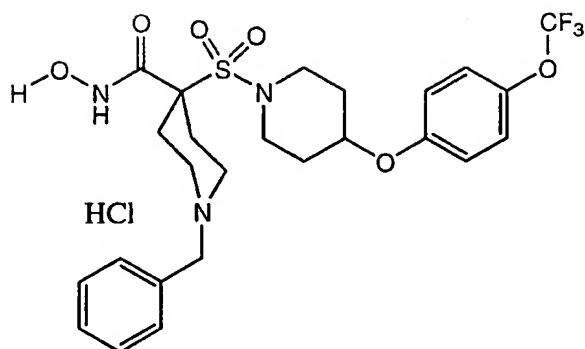
2)



10

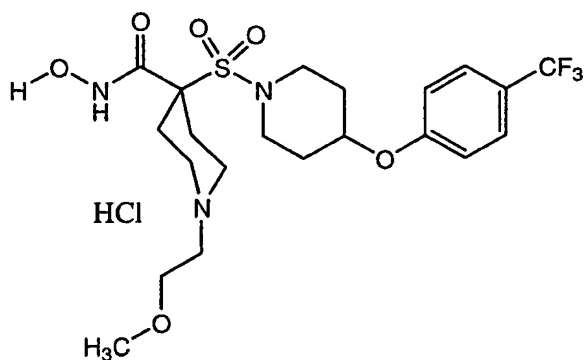
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

3)



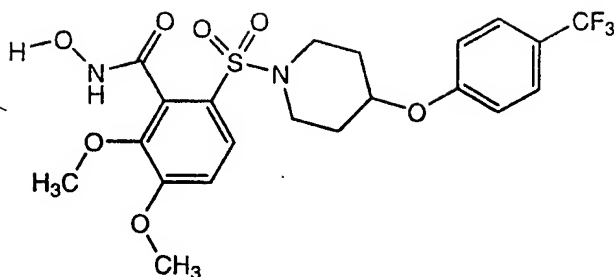
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

4)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

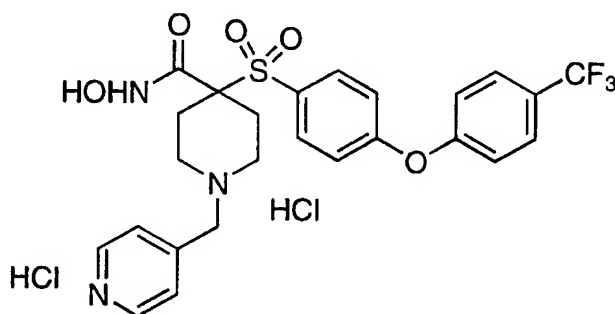
5)



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

5

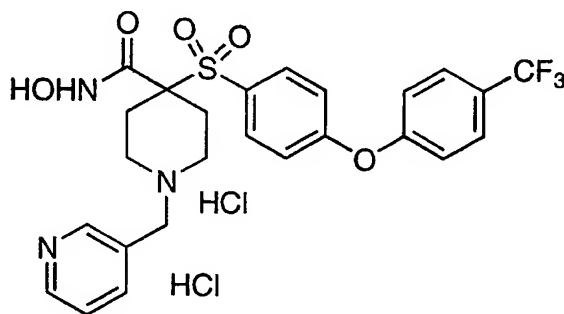
6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

10

7)

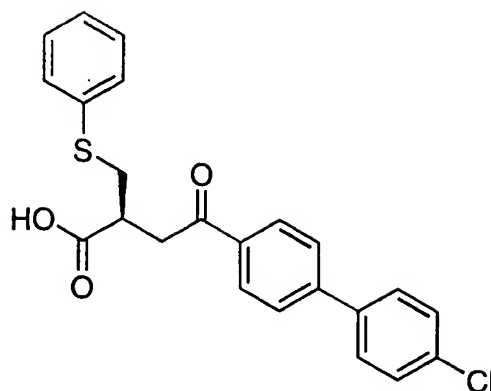


N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

15

- 42 -

10)

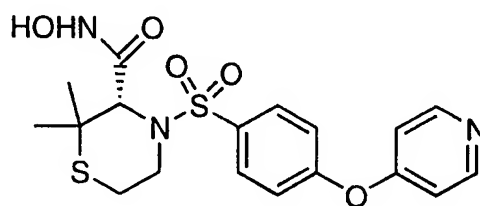


Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-

5

[(phenylthio)methyl]butanoic acid,

11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2
dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl] 3-
thiomorpholinecarboxamide,

10

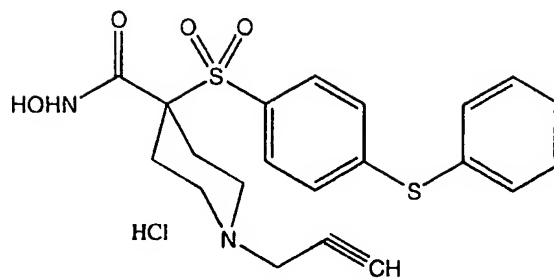
12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
6-demethyl-6-deoxy-4-

15

dedimethylaminotetracycline,

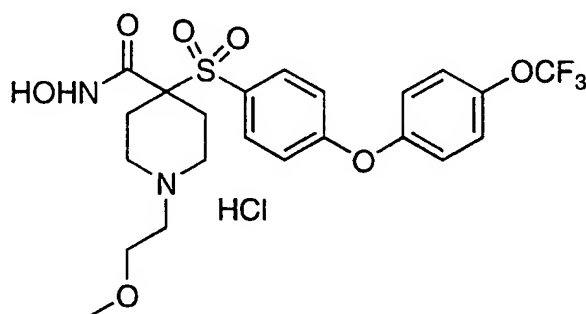
13) Chiroscience D-2163, 2- [1S- ((2R,S)-
acetylmercapto- 5- phthalimido]pentanoyl- L-
leucyl)amino- 3- methylbutyl]imidazole,

14)



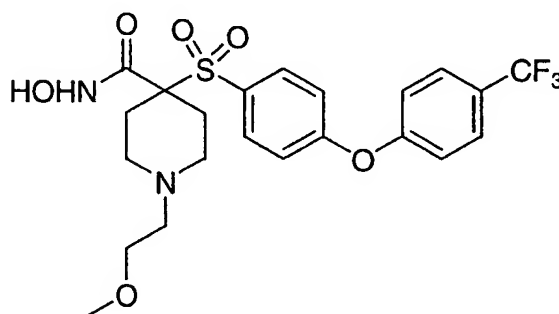
N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-
1-(2-propynyl)-4-piperidinecarboxamide
monohydrochloride,

15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide monohydrochloride,

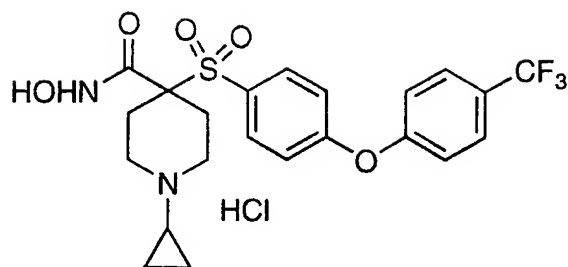
16)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide,

-424-

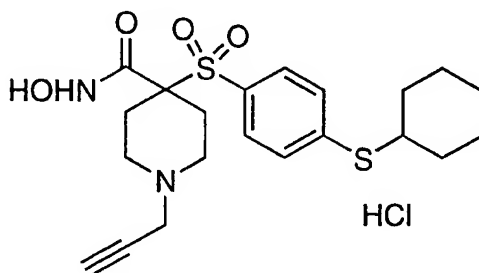
17)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

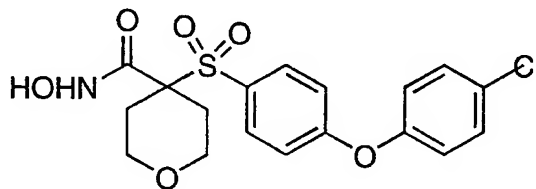
18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

10

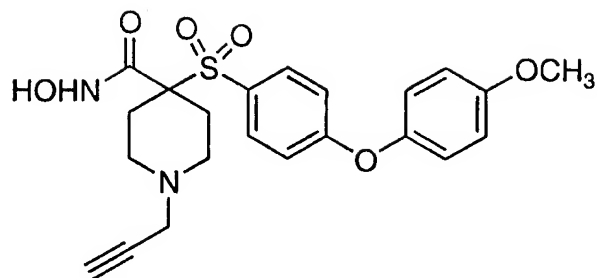
19)



4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

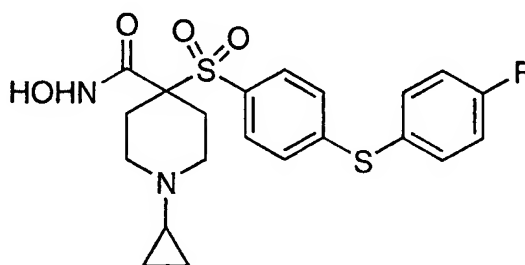
15

20)



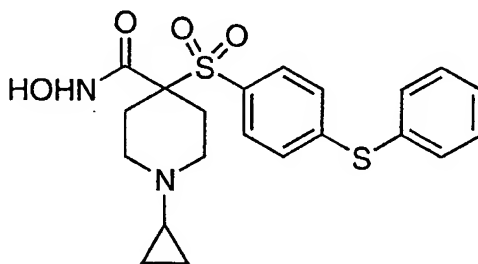
N-hydroxy-4-[[4-(4-
methoxyphenoxy)phenyl]sulfonyl]-1-(2-
propynyl)-4-piperidinecarboxamide,

21)



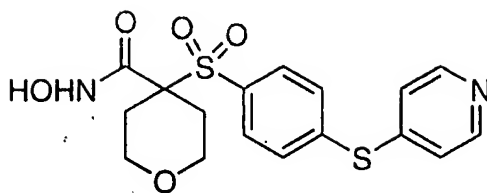
1-cyclopropyl-4-[[4-[(4-
fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-
4-piperidinecarboxamide,

22)



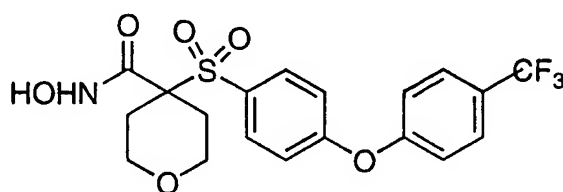
1-cyclopropyl-N-hydroxy-4-[[4-
(phenylthio)phenyl]sulfonyl]-4-
piperidinecarboxamide,

23)



tetrahydro-N-hydroxy-4-[[4-(4-
pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-
carboxamide, and

24)



tetrahydro-N-hydroxy-4-[[4-[4-
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-
pyran-4-carboxamide.

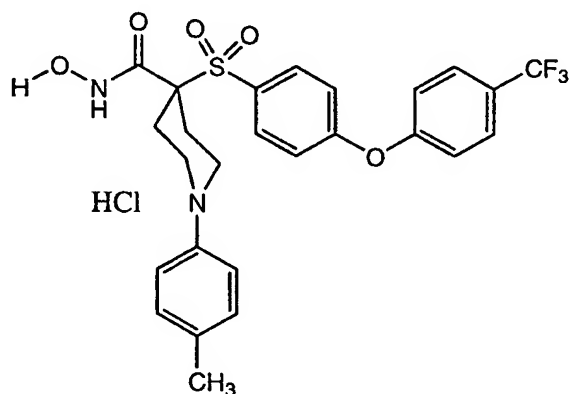
147. The method of Claim 146 comprising administering to said mammal a therapeutically-effective amount of a combination of an cyclooxygenase-2
- inhibitor, a matrix metalloproteinase inhibitor, and an antineoplastic agent, wherein the antineoplastic agent is selected from the group consisting of anastrozole, calcium carbonate, capecitabine, carboplatin, cisplatin, Cell Pathways CP-461, docetaxel, doxorubicin, etoposide, fluorouracil (5-FU), fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, mitoxantrone, paclitaxel, raloxifene, retinoic acid, tamoxifen, thiotepa, topotecan, toremifene, vinorelbine, vinblastine, vincristine, selenium (selenomethionine),

ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO).

148. The method of Claim 146 comprising
5 administering to said mammal a therapeutically-effective amount of a combination of radiation, a cyclooxygenase-2 inhibitor and a matrix metalloproteinase inhibitor.

149. A combination comprising a cyclooxygenase-2
10 inhibitor and a matrix metalloproteinase inhibitor, wherein said matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



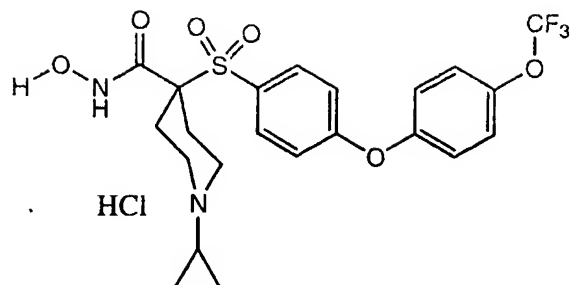
15

N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

20

2)

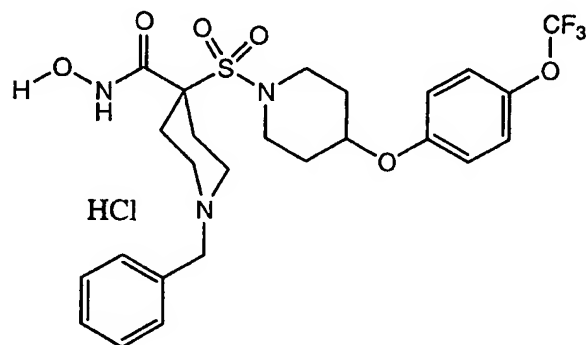
-428-



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

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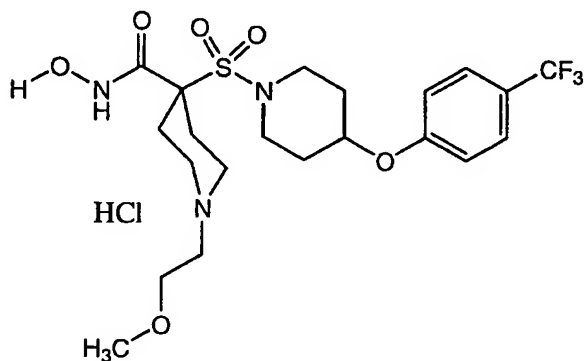
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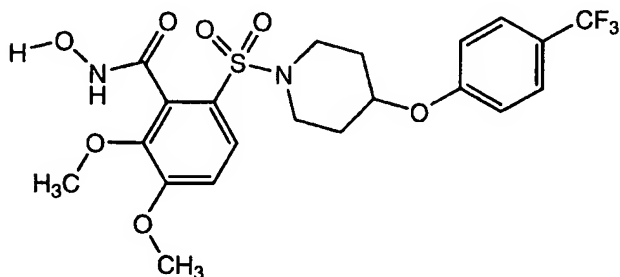
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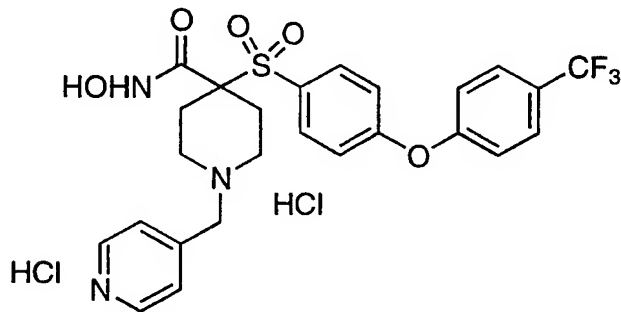
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N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

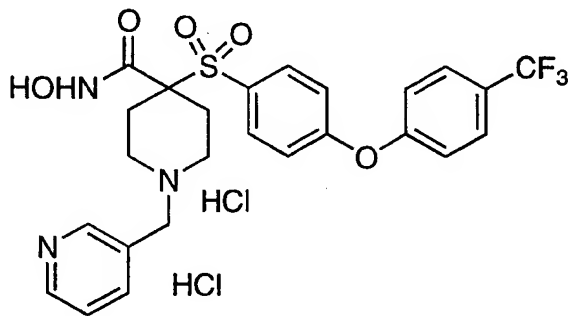
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7)

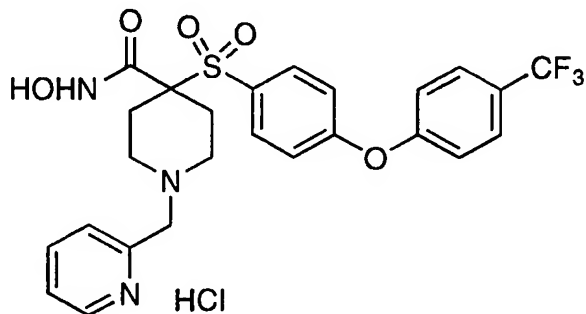


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-430-

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

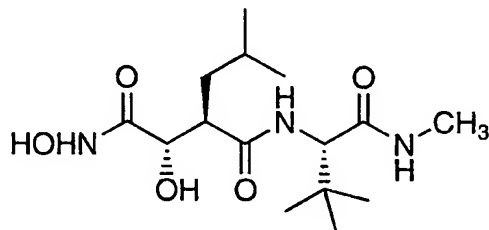
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N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

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9)

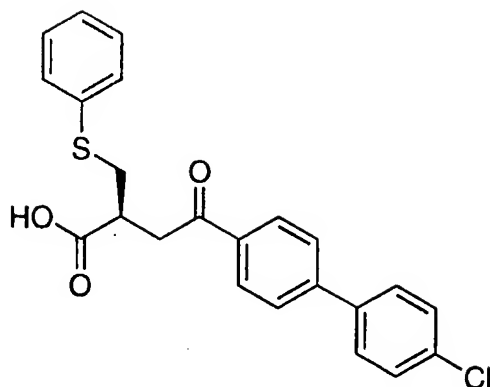


British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*), 2R*, 3S*]]-,

15

10)

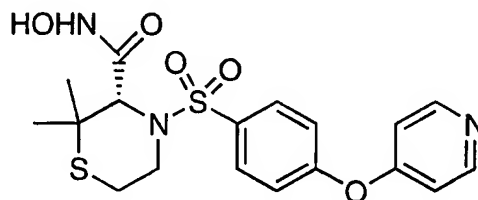
131



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-
iphenyl]- 4-yl)oxy]-2-
[(phenylthio)methyl]butanoic acid,

5

11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2
dimethyl-4-[[4-(4-
pyridinyloxy)phenyl]sulfonyl] 3-
thiomorpholinecarboxamide,

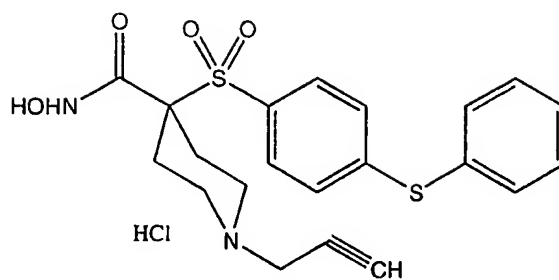
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12) CollaGenex Pharmaceuticals CMT-3 (Metastat),
6-demethyl-6-deoxy-4-
dedimethylaminotetracycline,

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13) Chiroscience D-2163, 2- [1S- ((2R,S)-
acetylmercapto- 5- phthalimido]pentanoyl- L-
leucyl)amino- 3- methylbutyl]imidazole,

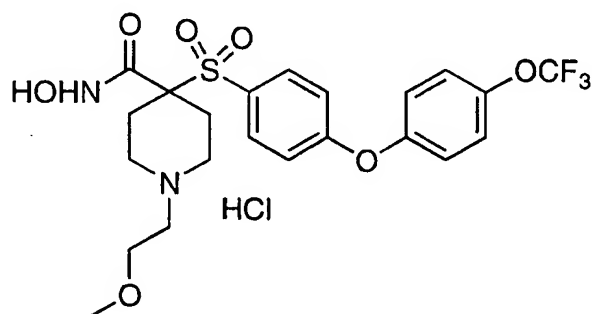
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N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-
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monohydrochloride,

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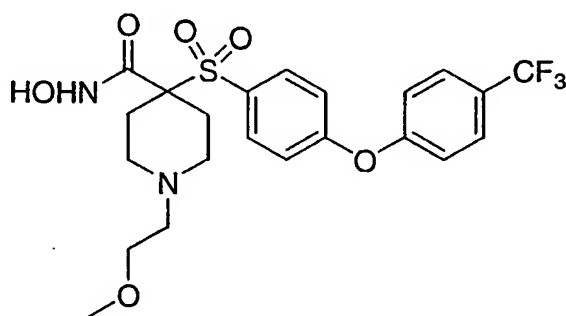
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N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-
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piperidinecarboxamide monohydrochloride,

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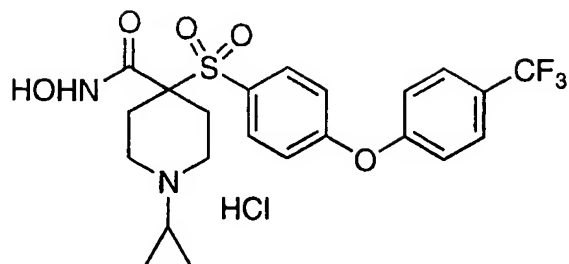
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(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-
piperidinecarboxamide,

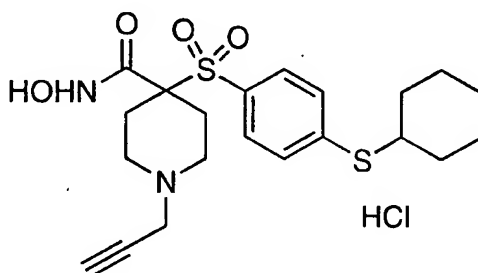
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17)



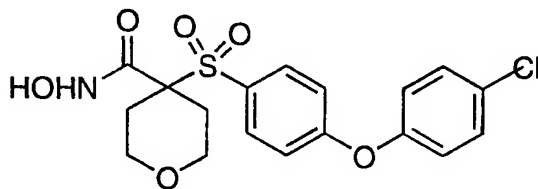
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

18)



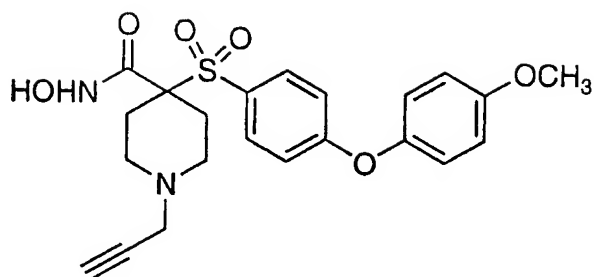
4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

19)



4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

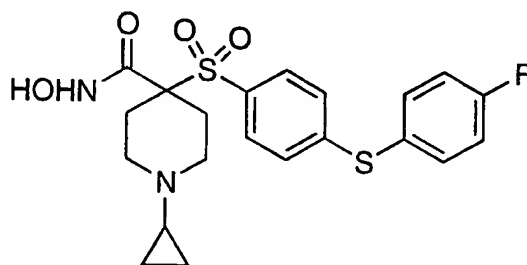
20)



N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

5

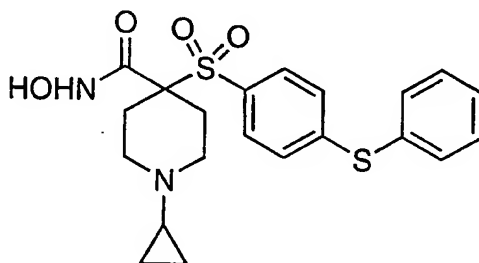
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1-cyclopropyl-4-[[4-(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

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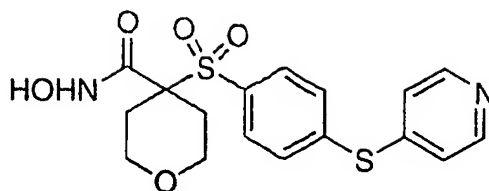
22)



1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

15

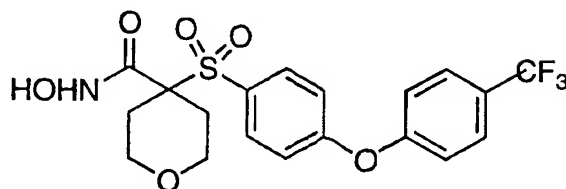
23)



tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

5

24)



tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide.

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 June 2000 (29.06.2000)

PCT

(10) International Publication Number
WO 00/37107 A3

- (51) International Patent Classification⁷: **A61K 45/06**, A61P 35/00, A61K 41/00
- (21) International Application Number: PCT/US99/30776
- (22) International Filing Date:
22 December 1999 (22.12.1999)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/113,786 23 December 1998 (23.12.1998) US
- (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): MCKEARN, John, P. [US/US]; 18612 Bable Meadows Drive, Glencoe, MO 63038 (US). GORDON, Gary [US/US]; 3282 University Avenue, Highland, IL 60035 (US). CUNNINGHAM, James, J. [CA/US]; 3733 North Bell Avenue, Chicago, IL 60618 (US). GATELY, Stephen, T. [CA/US]; 357 E. Shady Pines Court, Palatine, IL 60067-8800 (US). KOKI, Alane, T. [US/US]; 6689 Highway 185, Beaufort, MO 63013 (US). MASFERRER, Jaime, L. [CL/US]; 1213 Blairshire, Ballwin, MO 63011 (US).
- (74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).
- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
1 February 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/37107 A3

(54) Title: USE OF CYCLOOXYGENASE-2 INHIBITOR, A MATRIX METALLAPROTEINASE INHIBITOR, AN ANTINEOPLASTIC AGENT AND OPTIONALLY RADIATION AS A COMBINATION TREATMENT OF NEOPLASIA

(57) Abstract: The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor and an antineoplastic agent.

| | | |
|--|---|---|
| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K45/06 A61P35/00 A61K41/00 | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K A61P | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y | WO 98 16227 A (GORDON GARY B ; SEARLE & CO (US); SEIBERT KAREN (US); MASFERRER JAI) 23 April 1998 (1998-04-23) cited in the application page 3, line 1-8 | 1-145 |
| X | page 24, line 7 -page 29, line 6 claim 2 | 146-149 |
| Y | WO 97 48685 A (GLAXO GROUP LTD) 24 December 1997 (1997-12-24) page 10, line 6,7 claims 17-24 | 1-145 |
| --- -/-- | | |
| <div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div> | | |
| <div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> | | |
| Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">9 June 2000</div> | | Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">23. 06. 00</div> |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | | Authorized officer <div style="text-align: center; font-size: 1.2em;">Herrera, S</div> |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | US 5 629 343 A (HAGMANN WILLIAM ET AL) 13 May 1997 (1997-05-13) column 1, line 16-20 column 3, line 33-36 column 11, line 62-68 claims 7-13 --- | 1-145 |
| Y | US 5 672 583 A (CHAPMAN KEVIN ET AL) 30 September 1997 (1997-09-30) column 1, line 28-37 column 3, line 40-53 claims 10-17 --- | 1-145 |
| P,Y | EP 0 927 555 A (SANKYO CO) 7 July 1999 (1999-07-07) claim 42 page 24, line 28-34 --- | 1-145 |
| P,Y | WO 99 21583 A (WARNER LAMBERT CO ;SUN YI (US)) 6 May 1999 (1999-05-06) claims 1-8 --- | 1-145 |
| X | WO 98 22101 A (RAZ AMIRAM ;MASFERRER JAIME L (US); SEARLE & CO (US)) 28 May 1998 (1998-05-28) page 43, line 5-9 page 3, line 32-34 --- | 146-149 |
| E | EP 0 985 666 A (PFIZER) 15 March 2000 (2000-03-15) page 20, line 25-36 ----- | 146-149 |

INTERNATIONAL SEARCH REPORT

US 2010/0111111

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Present claims 1-149 relate to an extremely large number of possible products and/or methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products and/or methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the general concept, i.e. the triple combination treatment in general.

It is further pointed out that the second invention, i.e. the invention as claimed in claims 146-149 also lacks unity. The only feature being common for the compounds disclosed in claim 146 is that they are all MMP inhibitors.

Both wo

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-145

Use of a COX-2 inhibitor, a MMP inhibitor, an antineoplastic agent selected from a defined group and optionally radiation for the treatment or prevention of a neoplasia disorder and combinations (products) comprising said three active components

2. Claims: 146-149

Use of a COX-2 inhibitor and a MMP inhibitor selected from a defined group for the treatment or prevention of a neoplasia disorder and combinations (products) comprising said active components.

1997/10/15

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| WO 9816227 A | 23-04-1998 | AU 4904897 A BR 9712314 A CN 1244122 A CZ 9901171 A EP 0932402 A NO 991793 A | 11-05-1998 31-08-1999 09-02-2000 14-07-1999 04-08-1999 15-04-1999 |
| WO 9748685 A | 24-12-1997 | US 5990112 A AU 3102397 A US 5817751 A | 23-11-1999 07-01-1998 06-10-1998 |
| US 5629343 A | 13-05-1997 | AU 5292193 A WO 9407481 A | 26-04-1994 14-04-1994 |
| US 5672583 A | 30-09-1997 | AU 679474 B AU 5612994 A EP 0671911 A JP 8503475 T WO 9412169 A | 03-07-1997 22-06-1994 20-09-1995 16-04-1996 09-06-1994 |
| EP 0927555 A | 07-07-1999 | AU 9822598 A CN 1230407 A CZ 9804258 A HU 9803018 A JP 11246403 A NO 986089 A PL 330496 A JP 11279078 A JP 2000095685 A | 15-07-1999 06-10-1999 14-07-1999 28-10-1999 14-09-1999 25-06-1999 05-07-1999 12-10-1999 04-04-2000 |
| WO 9921583 A | 06-05-1999 | AU 1110799 A | 17-05-1999 |
| WO 9822101 A | 28-05-1998 | AU 7298298 A CZ 9901768 A EP 0941080 A NO 992309 A PL 333370 A | 10-06-1998 13-10-1999 15-09-1999 12-05-1999 06-12-1999 |
| EP 0985666 A | 15-03-2000 | JP 2000086630 A | 28-03-2000 |